

Catalytic Enantioselective Synthesis of Pyrrolizine Carboxylates using Isothiourea Catalysis: A Synthetic and Computational Study

Daniel G. Stark,^a Patrick Williamson,^a Emma R. Gayner,^b Stefania F. Musolino,^a Ryan W. F. Kerr,^a Alexandra M. Z. Slawin,^a Timothy J. C. O’Riordan,^c Stuart A. Macgregor^{*b} and A. D. Smith^{*a}

Table of Contents

| | | |
|------------|---|-----------|
| 1.1 | General Information | 2 |
| 1.2 | General Procedures | 3 |
| 1.3 | Experimental Information | 5 |
| 1.3.1 | Synthesis of Pyrrole Aldehydes..... | 5 |
| 1.3.2 | Synthesis of Pyrrolyl Enones..... | 6 |
| 1.3.3 | <i>N</i> -Alkylation of Pyrrolyl Enones..... | 10 |
| 1.3.4 | Hydrolysis of Pyrrolyl Enone-Esters..... | 15 |
| 1.3.5 | Intramolecular Isothiourea-Catalysed Michael Addition-Lactonisation | 20 |
| 1.3.6 | Intramolecular Isothiourea-Catalysed Michael Addition-Lactonisation/Ring Opening . | 21 |
| 1.3.7 | Derivatisations | 30 |
| 1.4 | Computational Details..... | 33 |
| 1.5 | Computed Reaction Profiles and Labelling Schemes..... | 34 |
| 1.6 | Computed Cartesian Coordinates (Å) and Energies (au) for all stationary points..... | 36 |
| 1.7 | References and Notes | 53 |
| 1.8 | ¹H NMR, ¹³C{¹H} NMR and HPLC Data for Novel Compounds | 53 |

1.1 General Information

Reactions involving moisture sensitive reagents were carried out under a nitrogen atmosphere using standard vacuum line techniques in addition to dry solvents. All glassware used was flame dried and cooled under vacuum. For moisture sensitive reactions, solvents (THF, CH₂Cl₂, toluene, hexane and Et₂O) were obtained anhydrous and purified by an alumina column (Mbraun SPS-800). Petrol is defined as petroleum ether 40-60 °C. All other solvents and commercial reagents were used as supplied without further purification unless stated otherwise.

Room temperature (rt) refers to 20-25 °C. Temperatures of 0 °C and -78 °C were obtained using ice/water and CO₂(s)/acetone baths respectively. Temperatures of 0 °C to -50 °C for overnight reactions were obtained using an immersion cooler (HAAKE EK 90). Reflux conditions were obtained using an oil bath equipped with a contact thermometer. *Under reduced pressure* refers to the use of a Büchi Rotavapor R-2000 rotary evaporator with a Vacubrand CVC₂ vacuum controller or a Heidolph Laborota 4001 rotary evaporator with a vacuum controller.

Analytical thin layer chromatography was performed on pre-coated aluminium plates (Kieselgel 60 F₂₅₄ silica). Plates were visualised under UV light (254 nm) or by staining with either phosphomolybdic acid or KMnO₄ followed by heating. Flash column chromatography was performed on Kieselgel 60 silica in the solvent system stated under a positive pressure of compressed air or on a Biotage® Isolera™ 4, using Biotage® Snap Ultra or Biotage® KP Sil columns under the solvent system stated.

¹H, ¹³C and ¹⁹F nuclear magnetic resonance (NMR) spectra were acquired on either a Bruker Avance 300 (300 MHz, ¹H, 75 MHz ¹³C, 282 MHz ¹⁹F), Bruker Avance II 400 (400 MHz, ¹H, 100 MHz ¹³C, 376 MHz ¹⁹F) or a Bruker Avance II 400 (500 MHz, ¹H, 125 MHz ¹³C, 470 MHz ¹⁹F) spectrometer at ambient temperature in the deuterated solvent stated. All chemical shifts are quoted in parts per million (ppm) relative to the residual solvent as the internal standard. All coupling constants, *J*, are quoted in Hz. Multiplicities are indicated by: s (singlet), d (doublet), t (triplet), q (quartet), sept (septet), ABq (AB quartet), sept (septet), oct (octet), m (multiplet), dd (doublet of doublets), ddd (doublet of doublet of doublets), dt (doublet of triplets), dq (doublet of quartets) and td (triplet of doublets). The abbreviation Ar is used to denote aromatic, Ph to denote phenyl, Bn to denote benzyl, py to denote pyridyl and br to denote broad.

Infrared spectra ($\nu_{\text{max}}/\text{cm}^{-1}$) were recorded on either a Perkin-Elmer Spectrum GX FT-IR spectrometer using a Shimadzu IRAffinity-1 using a Pike attenuated total reflectance (ATR) accessory. Only the characteristic peaks are quoted.

Melting points were recorded on an Electrothermal 9100 melting point apparatus and are uncorrected.

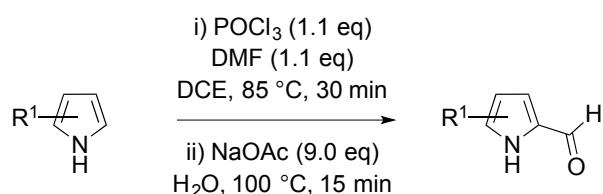
HPLC analyses were obtained on two separate machines; a Gilson HPLC consisting of a Gilson 305 pump, Gilson 306 pump, Gilson 811C dynamic mixer, Gilson 805 manometric module, Gilson 401C dilutor, Gilson 213XL sample injector and sample detection was performed with a Gilson 118 UV/vis detector while the temperature was assumed to be 20 °C; a Shimadzu HPLC consisting of a DGU-20A5 degasser, LC-20AT liquid chromatograph, SIL-20AHT autosampler, CMB-20A communications bus module, SPD-M20A diode array detector and a CTO-20A column oven which allowed the temperature to be set from 25-40 °C. Separation was achieved using DAICEL CHIRALCEL OD-H and OJ-H columns or DAICEL CHIRALPAK AD-H, AS-H, IA, IB, IC and ID columns. All chiral HPLC traces were compared to the authentic racemic spectrum prepared in analogous fashion.

Mass spectrometry (m/z) data were acquired by electrospray ionisation (ESI), electron impact (EI), atmospheric solids analysis probe (ASAP) or nanospray ionisation (NSI) either at the University of St Andrews or the EPSRC National Mass Spectrometry Service Centre, Swansea. At the University of St Andrews, low and high resolution ESI MS were carried out on a Micromass LCT spectrometer. At the EPSRC National Mass Spectrometry Service Centre, low resolution NSI MS was carried out on a Micromass Quattro II spectrometer and high resolution NSI MS on a Thermofisher LTQ Orbitrap XL spectrometer.

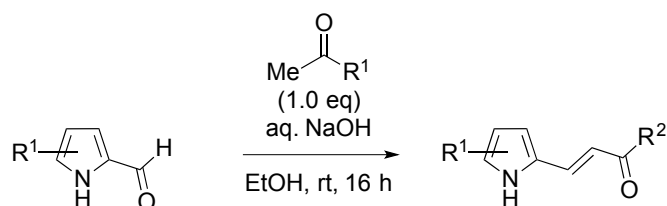
Optical rotations were measured on a Perkin Elmer Precisely/Model-341 polarimeter operating at the sodium D line with a 100 mm path cell at rt.

1.2 General Procedures

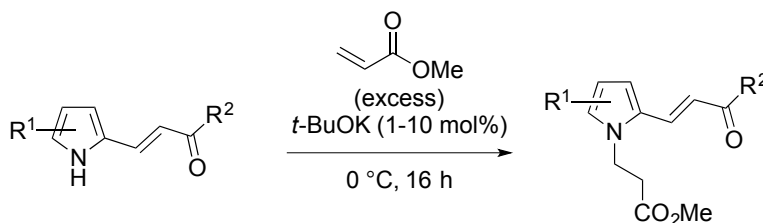
General procedure A: Preparation of Pyrrole 2-Carboxaldehydes



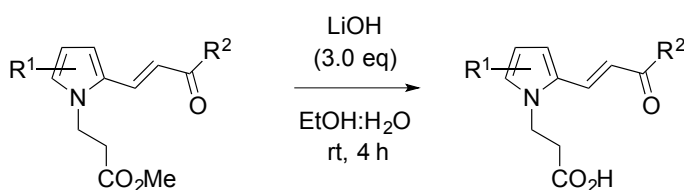
Following literature procedure,^[1] POCl₃ (1.1 eq) was added dropwise to DMF (1.1 eq) and the reaction was stirred for 15 min at rt. DCE (2.2 M in DMF) was added and the mixture cooled to 0 °C. A solution of requisite pyrrole (1.0 eq) in DCE (2.0 M in pyrrole) was added dropwise and the reaction was heated to 85 °C for 15 min before cooling to rt. A solution of aq. NaOAc (9.0 M, 9.0 eq) was added and the biphasic mixture stirred at 100 °C for 15 min. The reaction was cooled to rt and the phases separated. The aqueous phase was extracted with Et₂O (×3). The combined organics were washed with NaHCO₃, dried over MgSO₄ and concentrated under reduced pressure to provide the desired pyrrole 2-carboxaldehyde.

General Procedure B: Preparation of Pyrrolyl Enones

To an aqueous solution of NaOH (10% w/v in H₂O, 2.0 eq) was added dropwise to a solution of pyrrole-2-carboxaldehyde (1.0 eq) and the requisite ketone (1.0 eq) in ethanol (2.5 M in ketone). The reaction was stirred at rt for 16 h then acidified to pH 3 with aqueous HCl (2 M). The resultant precipitate was filtered, washed with cold ethanol to provide the desired enone product. Products were purified as described.

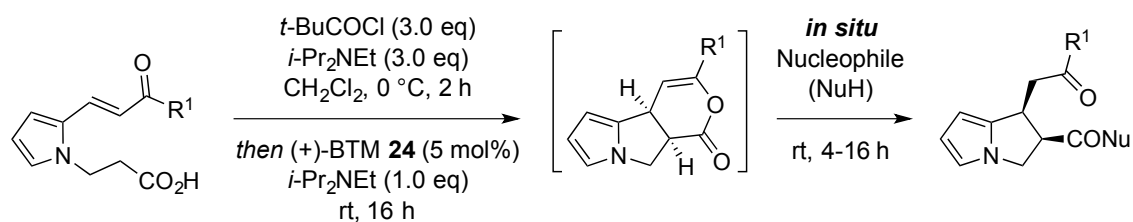
General Procedure C: N-Alkylation of Pyrrolyl Enones

To a solution of pyrrole enone (1.0 eq) in methyl acrylate (0.2 M in pyrrolyl enone) was added potassium *tert*-butoxide (1-10 mol%) and the reaction stirred at 70 °C for 16 h. The reaction was concentrated under reduced pressure, diluted with EtOAc, washed with brine (×3), dried over MgSO₄ and concentrated under reduced pressure to provide the crude product. Products were isolated by column chromatography in the solvent system stated.

General Procedure D: Hydrolysis of Pyrrolyl Enone-Esters

To a solution of pyrrolyl enone ester (1.0 eq) in H₂O/ethanol (1:1) was added LiOH.H₂O (4.0 eq) and reaction stirred at rt for 4 h. The reaction was then basified to pH 8 with aq. NaOH (2 M) and washed with Et₂O (×3). The aqueous layer was carefully acidified to pH 3 (caution: acidifying beyond pH 3 can lead to decomposition of product) with aq. HCl (2 M) and extracted with EtOAc (×3). Combined organic layers were washed with brine, dried over MgSO₄ and concentrated under reduced pressure to provide enone-acid products.

General Procedure E: Michael Addition-Lactonisation *in situ* Ring Opening

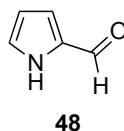


To a solution of pyrrolyl enone-acid (1.0 eq) in CH_2Cl_2 (0.1 M) was added pivaloyl chloride (3.0 eq) and $i\text{-Pr}_2\text{NEt}$ (3.0 eq) at $0\text{ }^\circ\text{C}$ and the reaction was allowed to warm to rt over 2 h. (+)-BTM **24** (5 mol%) and $i\text{-Pr}_2\text{NEt}$ (1.5 eq) was added and reaction stirred at rt overnight. The requisite nucleophile was then added and the reaction stirred until complete by TLC analysis. Reaction was quenched with aq. HCl (1 M) and extracted with CH_2Cl_2 ($\times 3$). Combined organic layers were dried over MgSO_4 and concentrated in vacuo to provide crude products. Products were isolated by column chromatography in the solvent system stated.

1.3 Experimental Information

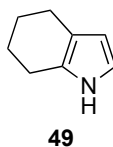
1.3.1 Synthesis of Pyrrole Aldehydes

1H-Pyrrole 2-carboxaldehyde



Following general procedure A, POCl_3 (2.0 mL, 21.5 mmol), DMF (1.7 mL, 21.5 mmol) and DCE (10 mL), pyrrole (1.4 mL, 20.2 mmol) in DCE (10 mL) and NaOAc (15 g, 182.9 mmol) in H_2O (20 mL) gave the title compound as a red oil (1.83 g, 96%); ^1H NMR (500 MHz, d_6 -DMSO) 6.33 (1H, m, pyrrolyl(4)*H*), 7.01 (1H, m, pyrrolyl(3)*H*), 7.18 (1H, m, pyrrolyl(5)*H*), 9.49 (1H, s, CHO), 11.13 (1H, br. s, NH). All data in accordance with literature.^[1]

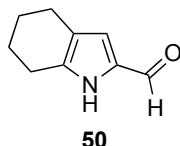
4,5,6,7-Tetrahydro-1H-indole



Following the literature procedure,^[2] $\text{NH}_2\text{OH}\cdot\text{HCl}$ (3.54 g, 50.9 mmol), cyclohexanone (5.28 mL, 50.9 mmol) and KOH (2.86 g, 50.9 mmol) were stirred in DMSO (42 mL) at $70\text{ }^\circ\text{C}$ for 30 min. The temperature was increased to $120\text{ }^\circ\text{C}$ and further KOH (7.15 g, 127.4 mmol) was added before the slow addition of a solution of DCE (20.5 mL, 259.5 mmol) in DMSO (65 mL) *via* syringe pump over 4 h. The reaction was cooled and added to aq. NH_4Cl (100 mL, 10% in H_2O) and extracted with Et_2O

(3×30 mL). The combined organics were washed with aq. KOH (1 M) then dried over MgSO₄ and concentrated under reduced pressure to give the crude product. Purification by column chromatography provided the title compound as pink solid (2.19 g, 35%); mp 50-51 °C {Lit.^[142] 51-52 °C}; ¹H NMR (500 MHz, CDCl₃) 1.74-1.87 (4H, m, C(5)H₂ and C(6)H₂), 2.57 (4H, dt, *J* 5.8, 20.2, C(4)H₂ and C(7)H₂), 6.00 (1H, br. s, C(3)H), 6.64 (1H, t, *J* 2.6, C(2)H), 7.70 (1H, NH). All data in accordance with literature.^[2]

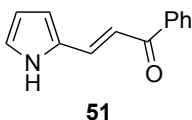
4,5,6,7-tetrahydro-1*H*-indole-2-carbaldehyde



Following general procedure A, POCl₃ (1.85 mL, 19.9 mmol), DMF (1.54 mL, 19.9 mmol) and DCE (9 mL), 4,5,6,7-tetrahydro-1*H*-indole **49** (1.4 mL, 20.2 mmol) in DCE (9 mL) and NaOAc (13.3 g, 162.3 mmol) in H₂O (18 mL) gave the title compound as a brown oil (2.21 g, 82%); ¹H NMR (500 MHz, CDCl₃) 1.71-1.83 (4H, m, C(5)H₂ and C(6)H₂), 2.51 (2H, t, *J* 6.1, C(4)H₂), 2.67 (2H, t, *J* 6.2, C(7)H₂), 6.73 (1H, s, C(3)H), 9.17 (1H, s, CHO), 10.5 (1H, br. s, NH). All data in accordance with literature.^[3]

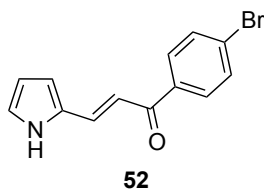
1.3.2 Synthesis of Pyrrolyl Enones

(*E*)-1-phenyl-3-(1*H*-pyrrol-2-yl)prop-2-en-1-one



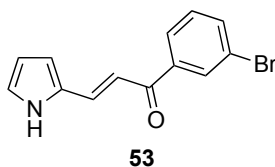
Following general procedure B, pyrrole carboxaldehyde (5.00 g, 52.6 mmol), aq. NaOH (5 mL, 10% w/v in H₂O) and acetophenone (6.14 mL, 52.6 mmol) in EtOH (21 mL) gave the title compound as a yellow solid (7.05 g, 68%); mp 135-137 °C; {lit.^[4] 136-137 °C}; ¹H NMR (500 MHz, CDCl₃) 6.34 (1H, s, pyrrolyl(4)H), 6.72 (1H, s, pyrrolyl(3)H), 7.00 (1H, s, pyrrolyl(5)H), 7.20 (1H, d, *J* 15.5, C(2)H), 7.47 (2H, m, C(1)Ar(3,5)H), 7.33 (1H, m, C(1)Ar(4)H), 7.78 (1H, d, *J* 15.5, C(3)H), 7.98 (2H, d, *J* 7.3, C(1)Ar(2,6)H). All data in accordance with literature.^[4]

(*E*)-1-(4-bromophenyl)-3-(1*H*-pyrrol-2-yl)prop-2-en-1-one



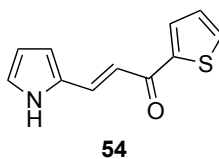
Following general procedure B, pyrrole carboxaldehyde (3.00 g, 31.5 mmol), aq. NaOH (3 mL, 10% w/v in H₂O) and 4'-bromoacetophenone (6.27 g, 31.5 mmol) in EtOH (13 mL) gave the title compound as a yellow solid (5.48 g, 63%); mp 182-184 °C; ν_{max} (ATR)/cm⁻¹ 975, 1330, 1539 (C-O), 3307 (C-H); ¹H NMR (500 MHz, *d*₆-DMSO) 6.35 (1H, dt, *J* 2.3, 3.6, pyrrolyl(4)*H*), 6.75 (1H, br. s, pyrrolyl(3)*H*), 7.17 (1H, br. s, pyrrolyl(5)*H*), 7.53 (1H, d, *J* 15.4, C(2)*H*), 7.61 (1H, d, *J* 15.5, C(3)*H*), 7.79 (2H, d, *J* 8.7, C(1)Ar(3,5)*H*), 7.96 (2H, d, *J* 8.6, C(1)Ar(2,6)*H*), 11.74 (1H, s, NH); ¹³C NMR (125 MHz *d*₆-DMSO) 110.8 (pyrrolylC(4)*H*), 114.1 (C(2)*H*), 116.8 (pyrrolylC(3)*H*), 124.6 (pyrrolylC(5)*H*), 126.6 (pyrrolylC(2)), 129.1 (C(1)ArC(4)), 129.9 (C(1)ArC(3,5)*H*), 131.8 (C(1)ArC(2,6)*H*), 134.7 (C(1)ArC(1)), 137.3 (C(3)*H*), 187.3 (C(1)); HRMS (APCI⁺), C₁₃H₁₀BrNO [M+H]⁺, requires 277.9998, found 277.9999 (+0.2 ppm).

(*E*)-1-(3-bromophenyl)-3-(1*H*-pyrrol-2-yl)prop-2-en-1-one



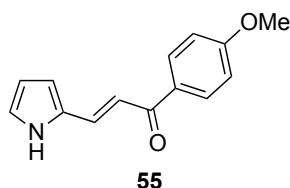
Following general procedure B, pyrrole carboxaldehyde (3.00 g, 31.5 mmol), aq. NaOH (3 mL, 10% w/v in H₂O) and 3'-bromoacetophenone (4.16 mL, 31.5 mmol) in EtOH (13 mL) gave the title compound as a crude mixture of *E/Z* isomers (85:15) (5.48 g, 63%). Data for (*E*)-isomer; ¹H NMR (500 MHz, *d*₆-DMSO) 6.21 (1H, m, pyrrolyl(4)*H*), 6.75 (1H, br. s, pyrrolyl(3)*H*), 7.16 (1H, br. s, pyrrolyl(5)*H*), 7.49-7.54 (2H, m, Ar(5)*H* and C(2)*H*), 7.61 (1H, d, *J* 15.3, C(3)*H*), 7.81-7.82 (1H, m, Ar(6)*H*), 7.99-8.00 (1H, m, Ar(4)*H*), 8.14-8.15 (1H, m, Ar(2)*H*), 11.7 (1H, s, NH). Due to instability this compound was used immediately without further characterisation.

(*E*)-3-(1*H*-pyrrol-2-yl)-1-(thiophen-2-yl)prop-2-en-1-one



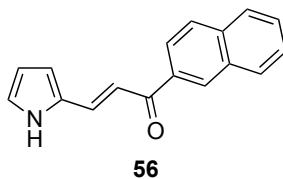
Following general procedure B, pyrrole carboxaldehyde (3.00 g, 31.5 mmol), aq. NaOH (3 mL, 10% w/v in H₂O) and 2-acetylthiophene (3.40 mL, 31.5 mmol) in EtOH (13 mL) gave the title compound as a yellow solid (4.55 g, 71%); mp 131-132 °C {Lit.^[5] 130 °C}; ¹H NMR (500 MHz, CDCl₃) 6.34-6.35 (1H, m, pyrrolyl(4)*H*), 6.73 (1H, s, pyrrolyl(3)*H*), 7.00-7.03 (2H, m, C(2)*H* and pyrrolyl(5)*H*), 7.16 (1H, dd, *J* 3.8, 4.9, C(1)Ar(3)*H*), 7.64 (1H, dd, *J* 1.0, 4.9, C(1)Ar(3)*H*), 7.76 (1H, d, *J* 15.4, C(3)*H*), 7.81 (1H, dd, *J* 1.1, 3.8, C(1)Ar(5)*H*). All data in accordance with literature.^[5]

(E)-1-(4-methoxyphenyl)-3-(1H-pyrrol-2-yl)prop-2-en-1-one



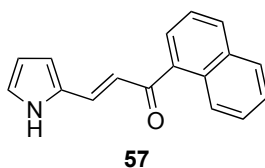
Following general procedure B, pyrrole carboxaldehyde (1.50 g, 15.8 mmol), aq. NaOH (1.5 mL, 10% w/v in H₂O) and 4'-methoxyacetophenone (2.37 g, 15.8 mmol) in EtOH (6.3 mL) gave the title compound as a yellow solid (2.30 g, 64%); mp 164-166 °C; ν_{max} (ATR)/cm⁻¹ 1134, 1539 (C-O), 3224 (C-H); ¹H NMR (500 MHz, CDCl₃) 3.88 (3H, s, C(1)ArOCH₃), 6.33 (1H, br. s, pyrrolyl(4)H), 6.71 (1H, s, pyrrolyl(3)H), 6.95-6.98 (3H, m, C(1)Ar(3,5)H and pyrrolyl(5)H), 7.16 (1H, d, *J* 15.5, C(2)H), 7.74 (1H, d, *J* 15.5, C(3)H), 8.00 (2H, d, *J* 8.8, C(1)Ar(2,6)H), 8.85 (1H, s, NH); ¹³C NMR (125 MHz) 55.6 (C(1)ArOCH₃), 111.6 (pyrrolylC(4)H), 113.9 (C(1)ArC(3,5)H), 114.9 (pyrrolylC(3)H), 115.7 (C(2)H), 122.9 (pyrrolylC(5)H), 129.5 (pyrrolylC(2)), 130.7 (C(1)ArC(2,6)H), 131.6 (C(1)ArC(1)), 133.8 (C(3)H), 163.3 (C(1)ArC(4)), 188.7 (C(1)); HRMS (APCI⁺), C₁₄H₁₃NO₂ [M+H]⁺, requires 226.0863, found 226.0862 (-0.2 ppm).

(E)-1-(Naphthalen-2-yl)-3-(1H-pyrrol-2-yl)prop-2-en-1-one



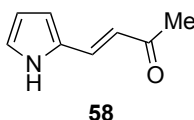
Following general procedure B, pyrrole carboxaldehyde (3.00 g, 31.5 mmol), aq. NaOH (3 mL, 10% w/v in H₂O) and 2-acetylnaphthalene (5.36 g, 31.5 mmol) in EtOH (20 mL) gave the title compound as a yellow solid (5.92 g, 76%); mp 158-160 °C; ν_{max} (ATR)/cm⁻¹ 820, 974, 1541 (C-O), 3284 (C-H); ¹H NMR (400 MHz, CDCl₃) 6.36 (1H, dd, *J* 1.1, 2.5, pyrrolyl(4)H), 6.75-6.76 (1H, m, pyrrolyl(3)H), 7.02 (1H, td, 1.4, 2.7, pyrrolyl(5)H), 7.30 (1H, d, *J* 15.5, C(2)H), 7.57 (2H, dddd, *J* 1.4, 6.9, 8.1, 19.5, ArH), 7.80 (1H, d, *J* 15.5, C(3)H), 7.88-7.97 (3H, m, ArH), 8.07 (1H, dd, *J* 1.8, 8.6, ArH), 8.49 (1H, s, ArH), 8.91 (1H, br. s, NH); ¹³C NMR (100 MHz) 111.7 (pyrrolylC(4)H), 115.6 (pyrrolylC(3)H), 116.0 (C(2)H), 123.2 (pyrrolylC(5)H), 124.7 (ArCH), 126.9 (ArCH), 128.0 (ArCH), 128.3 (ArCH), 128.6 (ArCH), 129.5 (pyrrolylC(2)), 129.6 (ArCH), 129.6 (ArCH), 132.7 (ArC), 134.5 (ArC), 135.5 (ArC), 136.1 (C(3)H), 190.2 (C(1)); HRMS (NSI⁺), C₁₇H₁₄NO₂ [M+H]⁺, requires 248.1068, found 248.1070 (-0.8 ppm).

(E)-1-(Naphthalen-1-yl)-3-(1H-pyrrol-2-yl)prop-2-en-1-one



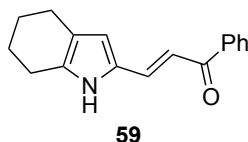
Following general procedure B, pyrrole carboxaldehyde (2.00 g, 21.0 mmol), aq. NaOH (2 mL, 10% w/v in H₂O) and 1-acetylnaphthalene (6.14 mL, 52.6 mmol) in EtOH (8.4 mL) gave the title compound as a yellow oil (1.06 g, 20%); ¹H NMR (300 MHz, CDCl₃) 6.30-6.33 (1H, m, pyrrolyl(4)*H*), 6.62 (1H, br. s, pyrrolyl(3)*H*), 6.89 (1H, d, *J* 15.9, C(2)*H*), 6.98 (1H, br. s, pyrrolyl(5)*H*), 7.45 (1H, d, *J* 16.0, C(3)*H*), 7.50-7.56 (3H, m, Ar*H*), 7.69 (1H, dd, *J* 1.2, 7.1, Ar*H*), 7.88-7.92 (1H, m, Ar*H*), 7.96-7.99 (1H, m, Ar*H*), 8.23-8.26 (1H, m, Ar*H*), 8.84 (1H, br. s, NH); ¹³C NMR (100 MHz) 111.7 (pyrrolylC(4)*H*), 116.4 (pyrrolylC(3)*H*), 121.0 (C(2)*H*), 124.2 (pyrrolylC(5)*H*), 124.8 (ArCH), 125.8 (ArCH), 126.5 (ArCH), 126.6 (ArCH), 127.3 (ArCH), 128.5 (ArCH), 129.0 (pyrrolylC(2)), 130.6 (ArC), 131.1 (ArCH), 133.9 (ArC), 136.9 (C(3)*H*), 137.7 (ArC), 196.7 (C(1)); HRMS (ESI⁺), C₁₇H₁₄NO [M+H]⁺, requires 248.1070, found 248.1071 (+0.4 ppm).

(E)-4-(1H-Pyrrol-2-yl)but-3-en-2-one



Following the procedure from Chimni and Mahajan,^[5] to a solution of pyrrole aldehyde (3.00 g, 31.5 mmol) and acetone (23.2 mL, 315.0 mmol) in H₂O (157.5 mL) was added pyrrolidine (0.77 mL, 9.45 mmol) and the reaction stirred at rt for 16 h. The reaction was quenched with HCl (1M in H₂O), extracted with CH₂Cl₂ (×3), dried over MgSO₄ and concentrated under reduced pressure to the title compound as a yellow solid (2.97 g, 70%); mp 115-117 °C {Lit.^[6] 117-120 °C}; ¹H NMR (300 MHz, CDCl₃) 2.33 (3H, s, C(1)*H*₃), 6.30-6.36 (2H, m, C(3)*H* and pyrrolyl(4)*H*), 6.60-6.62 (1H, m, pyrrolyl(3)*H*), 6.98-6.99 (1H, m, pyrrolyl(5)*H*), 7.41 (1H, d, *J* 16.2, C(4)*H*), 8.94 (1H, br. s, NH). All data in accordance with literature.^[6]

(E)-1-Phenyl-3-(4,5,6,7-tetrahydro-1H-indol-2-yl)prop-2-en-1-one

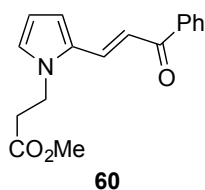


Following general procedure B, 4,5,6,7-tetrahydro-1H-indole-2-carbaldehyde **50** (2.21 g, 14.6 mmol), aq. NaOH (3 mL, 10% w/v in H₂O) and acetophenone (1.70 mL, 14.6 mmol) in EtOH (10 mL) gave crude product. The reaction mixture was neutralised to pH 7 with aq. HCl (1 M) and extracted with EtOAc (×3), dried over MgSO₄ and concentrated under reduced pressure. Purification by column

chromatography (EtOAc:hexane 7.5:92.5) gave the title compound as a brown oil (1.26 g, 34%); ^1H NMR (500 MHz, CDCl_3) 1.69-1.87 (4H, m, $\text{C}(3)\text{C}(5)\text{H}_2$ and $\text{C}(3)\text{C}(6)\text{H}_2$), 2.52 (2H, t, J 6.0, $\text{C}(3)\text{C}(4)\text{H}_2$), 2.64 (2H, t, J 6.1, $\text{C}(3)\text{C}(7)\text{H}_2$), 6.47 (1H, br. s, $\text{C}(3)\text{C}(3)\text{H}$), 7.01 (1H, d, J 15.4, $\text{C}(3)\text{H}$), 7.43-7.48 (2H, m, $\text{C}(1)\text{Ar}(3,5)\text{H}$), 7.50-7.58 (1H, m, $\text{C}(1)\text{Ar}(4)\text{H}$), 7.68 (1H, d, J 15.4, $\text{C}(2)\text{H}$), 7.95-7.97 (2H, m, $\text{C}(1)\text{Ar}(2,6)\text{H}$), 8.48 (1H, br. s, NH). All data in accordance with literature.^[7]

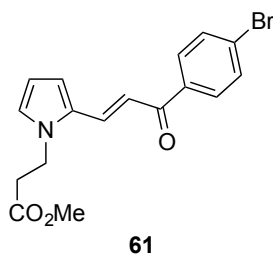
1.3.3 *N*-Alkylation of Pyrrolyl Enones

Methyl (*E*)-3-(2-(3-oxo-3-phenylprop-1-en-1-yl)-1*H*-pyrrol-1-yl)propanoate



Following general procedure C, pyrrolyl enone **51** (5.00 g, 25.6 mmol), potassium *tert*-butoxide (29 mg, 0.26 mmol) in methyl acrylate (135 mL) gave the title compound as a yellow oil (6.74 g, 93%); ν_{max} (ATR)/ cm^{-1} 1213, 1566, 1583, 1732 (ester $\text{C}=\text{O}$), 2951 (C-H); ^1H NMR (500 MHz, CDCl_3) 2.78 (2H, t, J 6.9, $\text{C}(2)\text{H}_2$), 3.69 (3H, s, CO_2CH_3), 4.39 (2H, t, J 6.9, $\text{C}(3)\text{H}_2$), 6.23-6.24 (1H, m, pyrrolyl(4)*H*), 6.85-6.86 (1H, m, pyrrolyl(3)*H*), 6.91-6.92 (1H, m, pyrrolyl(5)*H*), 7.33 (1H, d, J 15.1, pyrrolyl(2)*C*(2)*H*), 7.48-7.51 (2H, m, $\text{C}(\text{O})\text{Ar}(3,5)\text{H}$), 7.55-7.58 (1H, $\text{C}(\text{O})\text{Ar}(4)\text{H}$), 7.79 (1H, d, J 15.1, pyrrolyl(2)*C*(1)*H*), 8.01-8.02 (2H, $\text{C}(\text{O})\text{Ar}(2,6)\text{H}$); ^{13}C NMR (75 MHz, CDCl_3) 36.3 ($\text{C}(2)\text{H}_2$), 42.7 ($\text{C}(3)\text{H}_2$), 52.2 (CO_2CH_3), 110.4 (pyrrolyl $\text{C}(4)\text{H}$), 112.8 (pyrrolyl $\text{C}(3)\text{H}$), 117.2 (pyrrolyl(2)*C*(2)*H*), 127.2 (pyrrolyl $\text{C}(5)\text{H}$), 128.4 ($\text{C}(\text{O})\text{ArC}(2,6)\text{H}$), 128.7 ($\text{C}(\text{O})\text{ArC}(3,5)\text{H}$), 129.4 (pyrrolyl $\text{C}(2)$), 131.7 (pyrrolyl(2)*C*(1)*H*), 132.6 ($\text{C}(\text{O})\text{ArC}(4)\text{H}$), 138.8 ($\text{C}(\text{O})\text{ArC}(1)$), 171.2 (CO_2Me), 189.8 (pyrrolyl(2)*C*(3)); HRMS (NSI^+), $\text{C}_{17}\text{H}_{17}\text{NO}_3\text{Na}$ $[\text{M}+\text{Na}]^+$, requires 306.1101, found 306.1094 (−2.2 ppm).

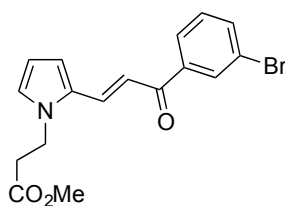
Methyl (*E*)-3-(2-(3-(4-bromophenyl)-3-oxoprop-1-en-1-yl)-1*H*-pyrrol-1-yl)propanoate



Following general procedure C, pyrrolyl enone **52** (3.00 g, 10.9 mmol), potassium *tert*-butoxide (57 mg, 0.26 mmol) in methyl acrylate (57 mL) gave the title compound as a yellow oil (3.51 g, 89%); ν_{max} (ATR)/ cm^{-1} 1170, 1678, 1732 (ester $\text{C}=\text{O}$), 2951 (C-H); ^1H NMR (400 MHz, CDCl_3) 2.77 (2H, t, J 6.9, $\text{C}(2)\text{H}_2$), 3.68 (3H, s, CO_2CH_3), 4.38 (2H, t, J 6.9, $\text{C}(3)\text{H}_2$), 6.23 (1H, m, pyrrolyl(4)*H*), 6.86 (1H, dd, J 1.1, 4.0, pyrrolyl(3)*H*), 6.92 (1H, dd, J 1.6, 2.5, pyrrolyl(5)*H*), 7.26 (1H, d, J 15.1, C

pyrrolyl(2)C(2)H), 7.62 (2H, d, J 8.7 C(O)Ar(3,5)H), 7.79 (1H, d, J 15.1, pyrrolyl(2)C(1)H), 7.88 (2H, d, J 8.7 C(O)Ar(2,6)H); ^{13}C NMR (100 MHz, CDCl_3) 36.3 ($\text{C}(2)\text{H}_2$), 42.6 (CO_2CH_3), 52.2 ($\text{C}(3)\text{H}_2$), 110.5 (pyrrolylC(4)H), 113.2 (pyrrolylC(3)H), 116.4 (pyrrolyl(2)C(2)H), 127.5 (pyrrolylC(5)H), 127.5 (C(O)ArC(4)), 129.3 (pyrrolylC(2)), 129.9 (C(O)ArC(2,6)H), 131.9 (C(O)ArC(3,5)H), 132.1 (pyrrolyl(2)C(1)H), 137.5 (C(O)ArC(1)), 171.1 (CO_2Me), 188.5 (pyrrolyl(2)C(3)); HRMS (NSI^+), $\text{C}_{17}\text{H}_{16}\text{Br}^{79}\text{NO}_3\text{Na}$ $[\text{M}+\text{Na}]^+$, requires 384.0206, found 384.0207 (+0.3 ppm).

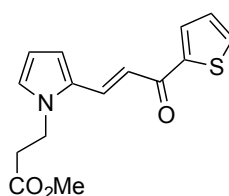
Methyl (*E*)-3-(2-(3-(3-bromophenyl)-3-oxoprop-1-en-1-yl)-1*H*-pyrrol-1-yl)propanoate



62

Following general procedure C, pyrrolyl enone **53** (3.00 g, 10.9 mmol), potassium *tert*-butoxide (122 mg, 1.09 mmol) in methyl acrylate (57 mL) gave the title compound as a yellow oil (1.62 g, 41%); ν_{max} (ATR)/ cm^{-1} 1560, 1578, 1734 (ester C=O), 2953 (C-H); ^1H NMR (500 MHz, CDCl_3) 2.78 (2H, t, J 6.9, $\text{C}(2)\text{H}_2$), 3.69 (3H, s, CO_2CH_3), 4.40 (2H, t, J 6.9, $\text{C}(3)\text{H}_2$), 6.24-6.25 (1H, m, pyrrolyl(4)H), 6.89 (1H, dd, J 1.3, 3.9, pyrrolyl(3)H), 6.93-6.94 (1H, m, pyrrolyl(5)H), 7.24 (1H, d, J 15.1, pyrrolyl(2)C(2)H), 7.37 (1H, t, J 7.9, C(O)Ar(5)H), 7.68 (1H, ddd, J 1.0, 1.9, 7.9, C(O)Ar(6)H), 7.79 (1H, d, J 15.1, pyrrolyl(2)C(1)H), 7.93 (1H, dt, J 1.2, 7.7, C(O)Ar(4)H), 8.13 (1H, m, C(O)Ar(2)H); ^{13}C NMR (125 MHz, CDCl_3) 36.3 ($\text{C}(2)\text{H}_2$), 42.6 (CO_2CH_3), 52.2 ($\text{C}(3)\text{H}_2$), 110.6 (pyrrolylC(4)H), 113.4 (pyrrolylC(3)H), 116.3 (pyrrolyl(2)C(2)H), 123.0 (C(O)ArC(3)), 126.8 (C(O)ArC(4)H), 127.7 (pyrrolylC(5)H), 129.2 (C(O)ArC(2)), 130.3 (C(O)ArC(5)H), 131.4 (C(O)ArC(2)H), 132.4 (pyrrolyl(2)C(1)H), 135.4 (C(O)ArC(6)H), 140.6 (C(O)ArC(1)), 171.1 (CO_2Me), 188.3 (pyrrolyl(2)C(3)); HRMS (NSI^+), $\text{C}_{17}\text{H}_{16}\text{Br}^{79}\text{NO}_3\text{Na}$ $[\text{M}+\text{Na}]^+$, requires 384.0206, found 384.0201 (-1.2 ppm).

Methyl (*E*)-3-(2-(3-oxo-3-(thiophen-2-yl)prop-1-en-1-yl)-1*H*-pyrrol-1-yl)propanoate

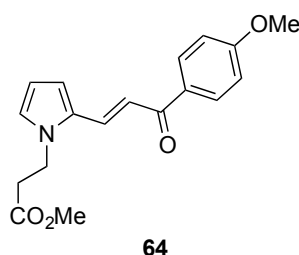


63

Following general procedure C, pyrrolyl enone **54** (3.00 g, 14.8 mmol), potassium *tert*-butoxide (166 mg, 1.48 mmol) in methyl acrylate (78 mL) gave the title compound as a yellow oil (1.28 g, 30%); ν_{max} (ATR)/ cm^{-1} 1410, 1570, 1635, 1734 (ester C=O), 2951, 3103 (C-H); ^1H NMR (300 MHz, CDCl_3)

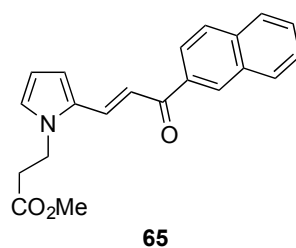
2.77 (2H, t, J 6.9, C(2) H_2), 3.69 (3H, s, CO₂CH₃), 4.39 (2H, t, J 6.9, C(3) H_2), 6.22-6.24 (1H, m, pyrrolyl(4) H), 6.85 (1H, dd, J 1.1, 4.0, pyrrolyl(3) H), 6.91 (1H, dd, J 1.6, 2.5, pyrrolyl(5) H), 7.15-7.21 (2H, m, C(O)thienyl(4) H and pyrrolyl(2)C(2) H), 7.64 (1H, dd, J 1.1, 5.0, C(O)thienyl(3) H), 7.77 (1H, d, J 15.0, pyrrolyl(2)C(1) H), 7.82 (1H, dd, J 1.1, 3.8, C(O)thienyl(5) H); ¹³C NMR (75 MHz, CDCl₃) 36.3 (C(2) H_2), 42.7 (CO₂CH₃), 52.2 (C(3) H_2), 110.4 (pyrrolylC(4) H), 112.9 (pyrrolylC(3) H), 117.0 (pyrrolyl(2)C(2) H), 127.3 (pyrrolylC(5) H), 128.3 (C(O)thienylC(5) H), 129.2 (pyrrolylC(2)), 131.0 (pyrrolyl(2)C(1) H), 131.2 (C(O)thienylC(4) H), 133.3 (C(O)thienylC(3) H), 146.2 (C(O)thienylC(2)), 171.2 (CO₂Me), 181.8 (pyrrolyl(2)C(3)); HRMS (NSI⁺), C₁₅H₁₅NO₃SNa [M+Na]⁺, requires 312.0665, found 312.0665 (0.0 ppm).

Methyl (*E*)-3-(2-(3-(4-methoxyphenyl)-3-oxoprop-1-en-1-yl)-1*H*-pyrrol-1-yl)propanoate



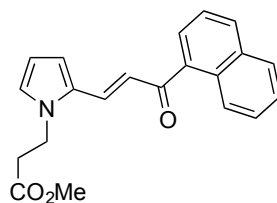
Following general procedure C, pyrrolyl enone **55** (2.00 g, 8.80 mmol), potassium *tert*-butoxide (10 mg, 0.088 mmol) in methyl acrylate (46 mL) gave the title compound as a yellow oil (2.56 g, 97%); ν_{max} (ATR)/cm⁻¹ 1168, 1581, 1589, 1732 (ester C=O), 2951 (C-H); ¹H NMR (300 MHz, CDCl₃) 2.78 (2H, t, J 6.9, C(2) H_2), 3.68 (3H, s, CO₂CH₃), 3.88 (3H, s, ArOCH₃), 4.39 (2H, t, J 6.9, C(3) H_2), 6.21 (1H, m, pyrrolyl(4) H), 6.83 (1H, dd, J 1.3, 3.9, pyrrolyl(3) H), 6.90 (1H, dd, J 1.6, 2.5, pyrrolyl(5) H), 6.97 (1H, d, J 8.9, C(O)Ar(3,5) H), 7.34 (1H, d, J 15.1, pyrrolyl(2)C(2) H), 7.76 (1H, d, J 15.1, pyrrolyl(2)C(1) H), 8.03 (2H, d, J 8.9, C(O)Ar(2,6) H); ¹³C NMR (75 MHz) 36.3 (C(2) H_2), 42.6 (C(3) H_2), 52.1 (CO₂CH₃), 55.6 (ArOCH₃), 110.2 (pyrrolylC(4) H), 112.4 (pyrrolylC(3) H), 113.9 (C(O)ArC(3,5) H), 117.2 (pyrrolyl(2)C(2) H), 126.9 (pyrrolylC(5) H), 129.5 (pyrrolylC(2)), 130.6 (C(O)ArC(2,6) H), 131.0 (pyrrolyl(2)C(1) H), 131.6 (C(O)ArC(1)), 163.3 (C(O)ArC(4)), 171.2 (CO₂Me), 188.1 (pyrrolyl(2)C(3)); HRMS (NSI⁺), C₁₈H₂₀NO₄ [M+H]⁺, requires 313.1387, found 313.1379 (-2.6 ppm).

Methyl (*E*)-3-(2-(3-(naphthalen-2-yl)-3-oxoprop-1-en-1-yl)-1*H*-pyrrol-1-yl)propanoate



Following general procedure C, pyrrolyl enone **56** (3.00 g, 12.1 mmol), potassium *tert*-butoxide (27 mg, 0.24 mmol) in methyl acrylate (64 mL) gave the title compound as a yellow oil (2.53 g, 63%); ν_{max} (ATR)/ cm^{-1} 1170, 1570, 1730 (ester C=O), 2951 (C-H); ^1H NMR (300 MHz, CDCl_3) 2.80 (2H, t, J 6.9, C(2) H_2), 3.69 (3H, s, CO_2CH_3), 4.42 (2H, t, J 6.9, C(3) H_2), 6.25-6.27 (1H, m, pyrrolyl(4) H), 6.92-6.94 (2H, m, pyrrolyl(3) H and pyrrolyl(5) H), 7.49 (1H, d, J 15.1, pyrrolyl(2)C(2) H), 7.52-7.63 (2H, m, $2\times\text{C(O)ArH}$), 7.82-8.02 (4H, m, pyrrolyl(2)C(1) H and $3\times\text{C(O)ArH}$), 8.11 (1H, dd, J 1.7, 8.6, C(O)Ar H), 8.53 (1H, br. s, C(O)Ar H); ^{13}C NMR (75 MHz, CDCl_3) 36.3 (C(2) H_2), 42.7 (C(3) H_2), 52.2 (CO_2CH_3), 110.4 (pyrrolylC(4) H), 112.9 (pyrrolylC(3) H), 117.3 (pyrrolyl(2)C(2) H), 124.6 (C(O)ArCH), 126.8 (C(O)ArCH), 127.2 (C(O)ArCH), 127.9 (C(O)ArCH), 128.3 (C(O)ArCH), 128.6 (C(O)ArCH), 129.5 (pyrrolylC(2)), 129.6 (C(O)ArCH), 129.6 (C(O)ArCH), 131.7 (pyrrolyl(2)C(1) H), 132.8 (C(O)ArC), 135.5 (C(O)ArC), 136.1 (C(O)ArC(1)), 171.2 (CO_2Me), 189.6 (pyrrolyl(2)C(3)); HRMS (NSI^+), $\text{C}_{21}\text{H}_{19}\text{NO}_3\text{Na}$ [$\text{M}+\text{Na}$] $^+$, requires 356.1257, found 356.1255 (−0.6 ppm).

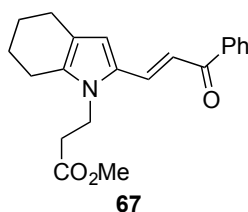
Methyl (*E*)-3-(2-(3-(naphthalen-1-yl)-3-oxoprop-1-en-1-yl)-1*H*-pyrrol-1-yl)propanoate



66

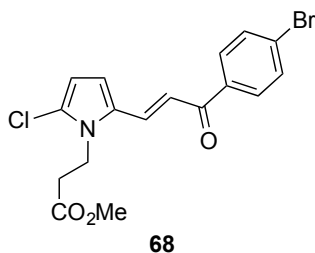
Following general procedure C pyrrolyl enone **57** (1.06 g, 4.47 mmol), potassium *tert*-butoxide (5 mg, 0.043 mmol) in methyl acrylate (22.5 mL) gave the title compound as a yellow oil (922 mg, 62%); ν_{max} (ATR)/ cm^{-1} 1280, 1570, 1732 (ester C=O), 2961 (C-H); ^1H NMR (500 MHz, CDCl_3) 2.70 (2H, t, J 6.8, C(2) H_2), 3.65 (3H, s, CO_2CH_3), 4.28 (2H, t, J 6.8, C(3) H_2), 6.21-6.22 (1H, m, pyrrolyl(4) H), 6.80 (1H, dd, J 1.2, 3.9, pyrrolyl(3) H), 6.90 (1H, br. s, pyrrolyl(5) H), 7.08 (1H, d, J 15.4, pyrrolyl(2)C(2) H), 7.50-7.57 (3H, m, Ar H), 7.63 (1H, d, J 15.4, 7.76-7.77 (1H, m, Ar H), 7.89 (1H, d, J 8.3, Ar H), 7.96 (1H, d, J 8.2, Ar H), 8.37 (1H, d, J 8.2, Ar H); ^{13}C NMR (125 MHz) 36.0 (C(2) H_2), 42.5 (C(3) H_2), 52.0 (CO_2CH_3), 110.4 (pyrrolylC(4) H), 113.3 (pyrrolylC(3) H), 122.0 (pyrrolyl(2)C(2) H), 124.6 (C(O)ArCH), 125.8 (C(O)ArCH), 126.4 (C(O)ArCH), 126.8 (C(O)ArCH), 127.2 (C(O)ArCH), 127.5 (C(O)ArCH), 128.4 (C(O)ArCH), 128.8 (pyrrolylC(2)), 130.5 (C(O)ArC), 131.3 (C(O)ArCH), 132.4 (pyrrolyl(2)C(1) H), 133.8 (C(O)ArC), 137.9 (C(O)ArC(1)), 170.9 (CO_2Me), 194.8 (pyrrolyl(2)C(3)); HRMS (NSI^+), $\text{C}_{21}\text{H}_{20}\text{NO}_3$ [$\text{M}+\text{H}$] $^+$, requires 334.1438, found 334.1439 (+0.3 ppm).

Methyl (*E*)-3-(2-(3-oxo-3-phenylprop-1-en-1-yl)-4,5,6,7-tetrahydro-1*H*-indol-1-yl)propanoate



Following general procedure C, pyrrolyl enone **58** (1.26 g, 5.01 mmol), potassium *tert*-butoxide (6 mg, 0.05 mmol) in methyl acrylate (26 mL) gave the title compound as a red oil (1.90 g, 95%); ν_{\max} (ATR)/ cm^{-1} 1549, 1581, 1732 (ester C=O), 2926 (C-H); ^1H NMR (500 MHz, CDCl_3) 1.71-1.76 (2H, m, C(3)C(6) H_2), 1.83-1.88 (2H, m, C(3)C(5) H_2), 2.52 (2H, m, C(3)C(4) H_2), 2.61 (2H, t, J 6.1, C(3)C(7) H_2), 2.70 (2H, t, J 6.5, C(2) H_2), 3.70 (3H, s, CO_2CH_3), 4.27 (2H, t, J 6.1, C(3) H_2), 6.69 (1H, s, C(3)pyrrolyl(3) H), 7.24 (1H, d, J 15.1, C(3)Ar(2)C(2) H), 7.46-7.49 (2H, m, C(O)Ar(3,5) H), 7.51-7.56 (1H, m, C(O)Ar(4) H), 7.79 (1H, d, J 15.0, C(3)Ar(2)C(1) H), 7.99-8.01 (2H, m, C(O)Ar(2,6) H); ^{13}C NMR (125 MHz, CDCl_3) 22.6 (C(3)C(7) H_2), 23.1 (C(3)C(4) H_2), 23.1 (C(3)C(5) H_2), 23.4 (C(3)C(6) H_2), 36.0 (C(2) H_2), 36.9 (C(3) H_2), 52.2 (CO_2CH_3), 111.8 (C(3)ArC(3) H), 114.8 (C(3)Ar(2)C(2) H), 121.1 (C(3)C(4a)), 128.3 (C(O)ArC(2,6) H), 128.3 (C(3)ArC(2)), 128.6 (C(O)ArC(3,5) H), 132.0 (C(3)Ar(2)C(1) H), 132.3 (C(O)ArC(4) H), 135.6 (C(3)Ar(2)C(2)), 139.2 (C(O)C(1)), 171.1 (CO_2Me), 189.7 (C(3)Ar(2)C(3)); HRMS (NSI^+), $\text{C}_{21}\text{H}_{23}\text{NO}_3\text{Na}$ [$\text{M}+\text{Na}$] $^+$, requires 360.1576, found 360.1541 (−9.7 ppm).

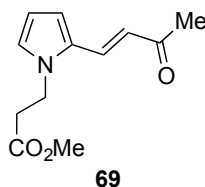
Methyl (*E*)-3-(2-(3-(4-bromophenyl)-3-oxoprop-1-en-1-yl)-5-chloro-1*H*-pyrrol-1-yl)propanoate



To a solution of pyrrolyl enone-ester **61** (2.20 g, 6.08 mmol) in CH_2Cl_2 (87 mL) at 0 °C was added *N*-chlorosuccinimide (975 mg, 7.30 mmol) portionwise. The reaction was allowed to warm to rt and stirred for 4 h. Reaction was quenched with saturated aq. NaCO_3 , extracted with CH_2Cl_2 ($\times 3$), dried over MgSO_4 and concentrated under reduced pressure to crude reaction mixture. Column chromatography (EtOAc:hexane 15:85) gave the title compound as a brown oil (600 mg, 25%); ν_{\max} (ATR)/ cm^{-1} 1555, 1587, 1739 (ester C=O), 2998 (C-H); ^1H NMR (300 MHz, CDCl_3) 2.74 (2H, t, J 6.9, C(2) H_2), 3.71 (3H, s, CO_2CH_3), 4.42 (2H, t, J 6.9, C(3) H_2), 6.21 (1H, d, J 4.2, pyrrolyl(4) H), 6.83 (1H, d, J 4.2, pyrrolyl(3) H), 7.26 (1H, d, J 15.1, pyrrolyl(2)C(2) H), 7.61-7.65 (2H, m, C(O)Ar(3,5) H), 7.76 (1H, d, J 15.1, pyrrolyl(2)C(1) H), 7.86-7.90 (2H, m, C(O)Ar(3,5) H); ^{13}C NMR (75 MHz, CDCl_3) 35.2 (C(2) H_2), 39.8 (CO_2CH_3), 52.2 (C(3) H_2), 109.7 (pyrrolylC(4) H), 112.6 (pyrrolylC(3) H), 116.5 (pyrrolyl(2)C(2) H), 127.8 (), 129.3 (pyrrolylC(2)), 129.9 (C(O)ArC(2,6) H), 132.0 (pyrrolyl(2)C(1) H),

132.0 (C(O)ArC(3,5)H), 137.4 (pyrrolylC(5)), 170.6 (CO₂Me), 188.4 (pyrrolyl(2)C(3)); C₁₇H₁₈⁷⁷BrClNO₃ [M+H]⁺, requires 397.9974, found 397.9970 (−1.1 ppm).

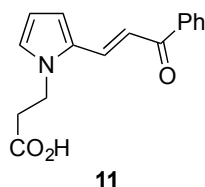
Methyl (E)-3-(2-(3-oxobut-1-en-1-yl)-1H-pyrrol-1-yl)propanoate



Following general procedure C pyrrolyl enone **58** (2.97 g, 22.0 mmol), potassium *tert*-butoxide (25 mg, 0.22 mmol) in methyl acrylate (116 mL) gave the title compound as a yellow oil (4.18 g, 90%); ν_{max} (ATR)/cm^{−1} 1174, 1627, 1740 (ester C=O), 2964 (C-H); ¹H NMR (300 MHz, CDCl₃) 2.30 (3H, s, pyrrolyl(2)C(4)H₃), 2.73 (2H, t, *J* 6.8, C(2)H₂), 3.66 (3H, s, CO₂CH₃), 4.32 (2H, t, *J* 6.8, C(3)H₂), 6.18 (1H, ddd, *J* 0.5, 2.7, 3.9, pyrrolyl(4)H), 6.50 (1H, d, *J* 15.6, pyrrolyl(2)C(2)H), 6.69-6.71 (1H, m, pyrrolyl(3)H), 6.86 (1H, dd, *J* 1.7, 2.5, pyrrolyl(5)H), 7.44 (1H, d, *J* 15.6, pyrrolyl(2)C(1)H); ¹³C NMR (75 MHz, CDCl₃) 28.3 (pyrrolyl(2)C(4)H₃), 36.2 (C(2)H₂), 42.5 (CO₂CH₃), 52.1 (C(3)H₂), 110.3 (pyrrolylC(4)H), 112.7 (pyrrolylC(3)H), 122.0 (pyrrolyl(2)C(2)H), 126.9 (pyrrolylC(5)H), 130.2 (pyrrolylC(2)), 171.1 (CO₂Me), 197.7 (pyrrolyl(2)C(3)); C₁₂H₁₆NO₃ [M+H]⁺, requires 222.1125, found 222.1123 (−0.9 ppm).

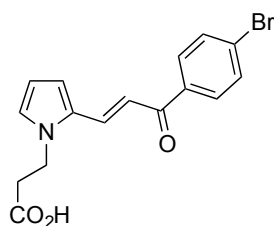
1.3.4 Hydrolysis of Pyrrolyl Enone-Esters

(E)-3-(2-(3-Oxo-3-phenylprop-1-en-1-yl)-1H-pyrrol-1-yl)propanoic acid



Following general procedure D, pyrrole enone ester **60** (8.00 g, 28.4 mmol) and LiOH (3.57 g, 85.2 mmol) in H₂O/ethanol (105 mL:105 mL) gave the title compound as a brown solid (4.96 g, 65%); mp 103-104 °C; ν_{max} (ATR)/cm^{−1} 1641 (C=O), 1732 (C=O), 3157 (C-H); ¹H NMR (500 MHz, CDCl₃) 2.85 (2H, t, *J* 7.1, C(2)H₂), 4.41 (2H, t, *J* 7.1, C(3)H₂), 6.25-6.26 (1H, m, pyrrolyl(4)H), 6.88 (1H, dd, *J* 1.3, 3.9, pyrrolyl(3)H), 6.94 (1H, m, pyrrolyl(5)H), 7.35 (1H, d, *J* 15.1, pyrrolyl(2)C(2)H), 7.48-7.51 (2H, m, C(O)Ar(3,5)H), 7.56-7.59 (1H, C(O)Ar(4)H), 7.86 (1H, d, *J* 15.1, pyrrolyl(2)C(1)H), 8.01-8.03 (2H, C(O)Ar(2,6)H); ¹³C NMR (100 MHz, CDCl₃) 36.1 (C(2)H₂), 42.5 (C(3)H₂), 52.2 (CO₂CH₃), 110.6 (pyrrolylC(4)H), 113.1 (pyrrolylC(3)H), 116.9 (pyrrolyl(2)C(2)H), 127.4 (pyrrolylC(5)H), 128.5 (C(O)ArC(2,6)H), 128.7 (C(O)ArC(3,5)H), 129.5 (pyrrolylC(2)), 132.4 (pyrrolyl(2)C(1)H), 132.8 (C(O)ArC(4)H), 138.7 (C(O)ArC(1)), 174.5 (CO₂H), 190.3 (pyrrolyl(2)C(3)); HRMS (NSI⁺), C₁₆H₁₅NO₃Na [M+Na]⁺, requires 292.0944, found 292.0947 (+1.0 ppm).

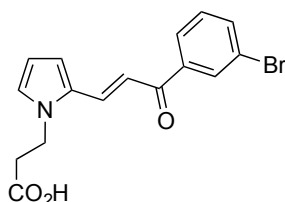
(E)-3-(2-(3-(4-Bromophenyl)-3-oxoprop-1-en-1-yl)-1H-pyrrol-1-yl)propanoic acid



12

Following general procedure D, pyrrole enone ester **61** (4.11 g, 11.4 mmol) and LiOH (1.44 g, 34.2 mmol) in H₂O/ethanol (48 mL:48 mL) gave the title compound as a yellow solid (3.57 g, 90%); mp 110-112 °C; ν_{\max} (ATR)/cm⁻¹ 1636 (C=O), 1726 (C=O), 3059 (C-H); ¹H NMR (500 MHz, d₆-DMSO) 2.69 (2H, t, *J* 6.9, C(2)*H*), 4.33 (2H, t, *J* 6.9, C(3)*H*), 6.20-6.22 (1H, m, pyrrolyl(4)*H*), 7.10 (1H, dd, *J* 4.0, 1.5, pyrrolyl(3)*H*), 7.14-7.16 (1H, m, pyrrolyl(5)*H*), 7.54 (1H, d, *J* 15.1, pyrrolyl(2)C(2)*H*), 7.73-7.78 (3H, m, pyrrolyl(2)C(1)*H* and C(O)Ar(3,5)*H*), 8.02-8.06 (2H, m, C(O)Ar(2,6)*H*), 12.4 (1H, br. s, OH); ¹³C NMR (125 MHz, d₆-DMSO) 36.0 (C(2)H₂), 42.0 (C(3)H₂), 110.0 (pyrrolylC(4)H), 113.6 (pyrrolylC(3)H), 115.7 (pyrrolyl(2)C(2)H), 128.0 (C(O)ArC(4)), 130.0 (pyrrolylC(2)), 130.2 (C(O)ArC(2,6)H), 131.7 (C(O)ArC(3,5)H), 132.40 (pyrrolyl(2)C(1)H), 137.2 (C(O)ArC(1)), 172.0 (CO₂H), 187.3 (pyrrolyl(2)C(3)); HRMS (NSI⁺), C₁₆H₁₅⁷⁹BrNO₃ [M+H]⁺, requires 348.0230, found 348.0233 (+0.9 ppm).

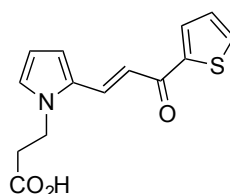
(E)-3-(2-(3-(3-Bromophenyl)-3-oxoprop-1-en-1-yl)-1H-pyrrol-1-yl)propanoic acid



13

Following general procedure D, pyrrole enone ester **62** (1.40 g, 3.87 mmol) and LiOH (487 mg, 11.6 mmol) in H₂O/ethanol (14 mL:14 mL) gave the title compound as a yellow solid (1.07 g, 81%); mp 138-140 °C; ν_{\max} (ATR)/cm⁻¹ 1584, 1728 (C=O), 3096 (C-H); ¹H NMR (400 MHz, d₆-DMSO) 2.69 (2H, t, *J* 6.9, C(2)H₂), 4.33 (2H, t, *J* 6.9, C(3)H₂), 6.21-6.22 (1H, m, pyrrolyl(4)*H*), 7.14-7.16 (2H, m, pyrrolyl(3)*H* and pyrrolyl(5)*H*), 7.50-7.57 (2H, m, pyrrolyl(2)C(2)*H* and C(O)Ar(5)*H*), 7.77 (1H, d, *J* 15.0, pyrrolyl(2)C(2)*H*), 7.83 (1H, dd, *J* 1.1, 8.0, C(O)Ar(5)*H*), 8.09 (1H, dt, *J* 1.1, 7.8, C(O)Ar(4)*H*), 8.23 (1H, t, *J* 1.8, C(O)Ar(2)*H*); ¹³C NMR (125 MHz, d₆-DMSO) 36.0 (C(2)H), 42.1 (C(3)H), 110.0 (pyrrolyl(4)*H*), 113.9 (pyrrolyl(3)*H*), 115.6 (pyrrolyl(2)C(2)*H*), 122.3 (C(O)ArC(3)), 127.2 (C(O)ArC(6)H), 128.2 (C(O)ArC(6)H), 128.9 (C(O)ArC(5)H), 130.6 (CO)ArC(2)H), 130.9 (pyrrolylC(2)), 132.7 (C(O)ArC(4)H), 135.2 (pyrrolyl(2)C(1)H), 140.3 (C(O)ArC(1)), 172.0 (CO₂H), 186.9 (pyrrolyl(2)C(3)); HRMS (NSI⁺), C₁₆H₁₅⁷⁹BrNO₃ [M+H]⁺, requires 276.0501, found 276.9886 (+0.9 ppm).

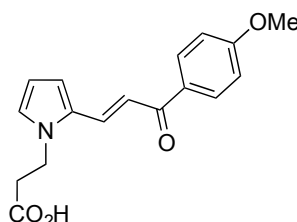
(E)-3-(2-(3-oxo-3-(Thiophen-2-yl)prop-1-en-1-yl)-1H-pyrrol-1-yl)propanoic acid



14

Following general procedure D, pyrrole enone ester **63** (1.28 g, 4.42 mmol) and LiOH (319 mg, 13.3 mmol) in H₂O/ethanol (16 mL:16 mL) gave the title compound as a yellow solid (1.12 g, 92%); mp 122-124 °C; ν_{\max} (ATR)/cm⁻¹ 1558, 1627 (C=O), 1726 (C=O), 2910 (C-H); ¹H NMR (400 MHz, CDCl₃) 2.84 (2H, t, *J* 7.2, C(2)H₂), 4.33 (2H, t, *J* 6.9, C(3)H₂), 6.24-6.26 (1H, dd, *J* 2.7, 3.5, pyrrolyl(4)H), 6.88 (1H, dd, *J* 1.2, 4.0, pyrrolyl(3)H), 6.94 (1H, dd, 1.6, 2.5, pyrrolyl(5)H), 7.16-7.22 (2H, m, pyrrolyl(2)C(2)H and C(O)thienyl(4)H), 7.66 (1H, dd, *J* 1.1, 4.9, C(O)thienyl(3)H), 7.84-7.88 (2H, m, C(O)thienyl(5)H and pyrrolyl(2)C(1)H); ¹³C NMR (100 MHz, CDCl₃) 36.1 (C(2)H₂), 42.5 (C(3)H₂), 110.7 (pyrrolylC(4)H), 113.1 (pyrrolylC(3)H), 116.8 (pyrrolyl(2)C(2)H), 127.5 (pyrrolylC(5)H), 128.4 (C(O)thienylC(4)H), 129.3 (pyrrolylC(2)), 131.6 (C(O)thienylC(5)H), 131.7 (pyrrolyl(2)C(1)H), 133.7 (C(O)thienylC(3)H), 146.0 (C(O)thienylC(2)), 174.6 (CO₂H), 182.3 (pyrrolyl(2)C(3)); HRMS (NSI⁻), C₁₄H₁₂NO₃S [M-H]⁻, requires 274.0543, found 274.0536 (-2.7 ppm).

(E)-3-(2-(3-(4-Methoxyphenyl)-3-oxoprop-1-en-1-yl)-1H-pyrrol-1-yl)propanoic acid

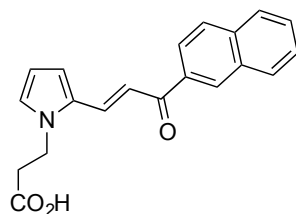


15

Following general procedure D, pyrrole enone ester **64** (2.43 g, 7.75 mmol) and LiOH (978 mg, 23.3 mmol) in H₂O/ethanol (29 mL:29 mL) gave the title compound as a brown solid (1.90 g, 82%); mp 147-148 °C; ν_{\max} (ATR)/cm⁻¹ 1634 (C=O), 1730, (C=O), 3084 C-H); ¹H NMR (500 MHz, d₆-DMSO) 2.69 (2H, t, *J* 6.9, C(2)H₂), 3.86 (3H, s, OCH₃), 4.33 (2H, t, *J* 6.9, C(3)H₂), 6.18-6.20 (1H, m, pyrrolyl(4)H), 7.04-7.08 (3H, m, pyrrolyl(3)H and C(O)Ar(3,5)H), 7.11-7.12 (1H, m, pyrrolyl(5)H), 7.56 (1H, d, *J* 15.1, pyrrolyl(2)C(2)H), 7.70 (1H, d, *J* 15.1, pyrrolyl(2)C(1)H), 8.07-8.12 (m, 2H, C(O)ArC(2,6)H), 12.38 (1H, br. s., OH); ¹³C NMR (125 MHz, d₆-DMSO) 36.0 (C(2)H₂), 42.1 (C(3)H₂), 55.5 (OCH₃), 109.6 (pyrrolylC(4)H), 112.9 (pyrrolylC(3)H), 113.9 (C(O)ArC(3,5)H), 116.3 (pyrrolyl(2)C(2)H), 127.3 (pyrrolylC(5)H), 128.94 (pyrrolylC(2)), 130.5 (C(O)ArC(2,6)H) 131.0 (C(O)ArC(1)), 131.1 (pyrrolyl(2)C(1)H), 162.8 (C(O)ArC(1)), 172.0 (C(1)), 186.7

(pyrrolylC(2)C(3)); HRMS (NSI⁺), C₁₇H₁₆NO₄ [M-H]⁻, found 298.1085, requires 298.1081 (-1.3 ppm).

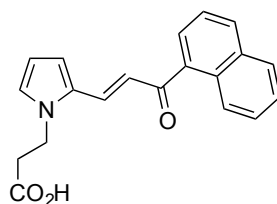
(E)-3-(2-(3-(Naphthalen-2-yl)-3-oxoprop-1-en-1-yl)-1H-pyrrol-1-yl)propanoic acid



16

Following general procedure D, pyrrolyl enone ester **65** (2.53 g, 7.57 mmol) and LiOH (952 mg, 22.7 mmol) in H₂O/ethanol (28 mL:28 mL) gave the title compound as a brown solid (1.35 g, 56%); mp 120-122 °C; ν_{max} (ATR)/cm⁻¹ 1556, 1728 (C=O), 3047 (C-H); ¹H NMR (400 MHz, *d*₆-DMSO) 2.72 (2H, t, *J* 6.9, C(2)H₂), 4.36 (2H, t, *J* 6.9, C(3)H₂), 6.23-6.24 (1H, m, pyrrolyl(4)H), 7.12-7.16 (2H, m, pyrrolyl(3)H and pyrrolyl(5)H), 7.61-7.69 (2H, m, ArH), 7.74 (1H, d, *J* 15.1, pyrrolyl(2)C(2)H), 7.81 (1H, d, *J* 15.1, pyrrolyl(2)C(1)H), 7.96-8.05 (2H, m, ArH), 8.10-8.16 (2H, m, ArH), 8.83 (1H, s, ArH), 12.4 (1H, br. s, CO₂H); ¹³C NMR (100 MHz, *d*₆-DMSO) 36.0 (C(2)H₂), 42.1 (C(3)H₂), 109.8 (pyrrolylC(4)H), 113.3 (pyrrolylC(3)H), 116.3 (pyrrolyl(2)C(2)H), 124.2 (C(O)ArCH), 126.9 (C(O)ArCH), 127.7 (C(O)ArCH), 127.7 (C(O)ArCH), 128.3 (C(O)ArCH), 128.4 (pyrrolylC(5)H), 129.0 (C(O)ArCH), 129.5 (C(O)ArCH), 129.6 (pyrrolylC(2)), 131.8 (C(O)ArC), 132.4 (pyrrolyl(2)C(1)H), 134.9 (C(O)ArC), 135.5 (C(O)ArC), 172.0 (CO₂H), 188.2 (pyrrolyl(2)C(3)); HRMS (NSI⁻), C₂₀H₁₆NO₃ [M-H]⁻, requires 318.1136, found 318.1131 (-1.5 ppm).

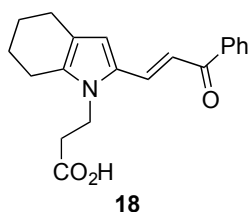
(E)-3-(2-(3-(Naphthalen-1-yl)-3-oxoprop-1-en-1-yl)-1H-pyrrol-1-yl)propanoic acid



17

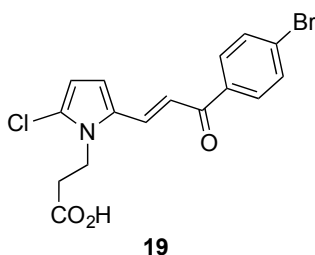
Following general procedure D, pyrrolyl enone ester **66** (1.68 g, 5.04 mmol) and LiOH (634 mg, 15.1 mmol) in H₂O/ethanol (19 mL:19 mL) gave the title compound as a crude residue of 80% purity; ¹H NMR (400 MHz, *d*₆-DMSO) 2.65 (2H, t, *J* 6.9, C(2)H₂), 4.24 (2H, t, *J* 6.9, C(3)H₂), 6.18-6.19 (1H, m, pyrrolyl(4)H), 6.98-6.98 (1H, m, pyrrolyl(3)H), 7.13-7.14 (1H, m, pyrrolyl(5)H), 7.17 (1H, d, *J* pyrrolyl(2)C(2)H), 7.55-7.63 (5H, m, C(O)ArH ×3 and pyrrolyl(2)C(1)H), 7.88-7.89 (1H, m, C(O)ArH), 8.02-8.03 (1H, m, C(O)ArH), 8.10-8.11 (1H, m, C(O)ArH), 8.29-8.30 (1H, m, C(O)ArH), 12.3 (1H, br. s, CO₂H). The crude residue was carried forward immediately into the next step without further characterisation.

(E)-3-(2-(3-oxo-3-phenylprop-1-en-1-yl)-4,5,6,7-tetrahydro-1H-indol-1-yl)propanoic acid



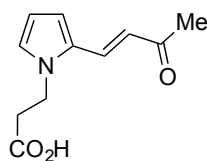
Following general procedure D, pyrrolyl enone ester **67** (1.90 g, 5.63 mmol) and LiOH (709 mg, 16.9 mmol) in H₂O/ethanol (21 mL:21 mL) gave the title compound as a crude residue of 80% purity; ¹H NMR (400 MHz, *d*⁶-DMSO) 1.74-1.77 (2H, m, indolyl(6)*H*₂), 1.81-1.87 (2H, m, indolyl(5)*H*₂), 2.50-2.53 (2H, m, indolyl(4)*H*₂), 2.59-2.62 (2H, m, indolyl(7)*H*₂), 2.70 (2H, t, *J* 6.8, C(2)*H*₂), 4.26 (2H, t, *J* 6.8, C(3)*H*₂), 6.69 (1H, s, indolyl(3)*H*), 7.23 (1H, d, *J* 14.9, indolyl(2)C(2)*H*), 7.44-7.54 (3H, m, C(O)Ar(3,5)*H* and C(O)Ar(4)*H*), 7.79 (1H, d, *J* 14.9, indolyl(2)C(1)*H*), 7.98-8.00 (2H, m, C(O)Ar(2,6)*H*). The crude residue was carried forward immediately into the next step without further characterisation.

(E)-3-(2-(3-(4-bromophenyl)-3-oxoprop-1-en-1-yl)-5-chloro-1H-pyrrol-1-yl)propanoic acid



Following general procedure D, pyrrolyl enone ester **68** (496 mg, 1.24 mmol) and LiOH (156 mg, 3.72 mmol) in H₂O/ethanol (4.6 mL:4.6 mL) gave the title compound as a brown solid (327 mg, 69%); mp 160-162 °C; *v*_{max} (ATR)/cm⁻¹ 1558, 1575, 1641 (C=O), 1741 (C=O), 3086 (C-H); ¹H NMR (300 MHz, CDCl₃) 2.79 (2H, t, *J* 6.9, C(2)*H*₂), 4.46 (2H, t, *J* 6.9, C(3)*H*₂), 6.23 (1H, d, *J* 4.2, pyrrolyl(4)*H*), 6.87 (1H, d, *J* 4.1, pyrrolyl(3)*H*), 7.28 (1H, d, *J* 15.1, pyrrolyl(2)C(2)*H*), 7.63 (2H, d, *J* 8.5, C(O)Ar(3,5)*H*), 7.85-7.90 (3H, m, pyrrolyl(2)C(1)*H* and C(O)Ar(2,6)*H*); ¹³C NMR (125 MHz, CDCl₃) 34.8 (C(2)*H*₂), 39.5 (C(3)*H*₂), 109.8 (pyrrolylC(4)*H*), 112.8 (pyrrolylC(3)*H*), 116.3 (pyrrolyl(2)C(2)*H*), 122.5 (C(O)ArC(4)), 128.0 (C(O)ArC(1)), 129.4 (), 130.0 (C(O)ArC(3,5)*H*), 132.0 (C(O)ArC(2,6)*H*), 132.7 (pyrrolyl(2)C(1)*H*), 137.2 (pyrrolylC(5)), 173.1 (CO₂H), 188.9 (pyrrolyl(2)C(3)O); HRMS (NSI⁻, C₁₆H₁₂Br⁷⁹Cl³⁵NO₃ [M-H]⁻, requires 379.9694, found 379.9695 (0.0 ppm).

(E)-3-(2-(3-Oxobut-1-en-1-yl)-1H-pyrrol-1-yl)propanoic acid

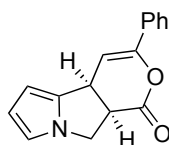


20

Following general procedure D, pyrrolyl enone ester **69** (4.41 g, 19.9 mmol) and LiOH (2.51 g, 59.7 mmol) in H₂O/ethanol (74 mL:74 mL) gave the title compound as a brown solid (1.12 g, 92%); mp 122-124 °C; ν_{\max} (ATR)/cm⁻¹ 1591, 1714 (C=O), 2906 (C-H); ¹H NMR (500 MHz, CDCl₃) 2.27 (3H, s, C(O)CH₃), 2.65 (2H, t, *J* 6.8, C(2)H₂), 4.30 (2H, d, *J* 6.8 C(3)H₂), 6.13-6.15 (1H, m, pyrrolyl(4)H), 6.45 (1H, d, *J* 15.6, pyrrolyl(2)C(2)H), 6.77 (1H, dd, *J* 1.4, 3.9, pyrrolyl(3)H), 7.06-7.07 (1H, m, pyrrolyl(5)H), 7.53 (1H, d, *J* 15.9, pyrrolyl(2)C(1)H); ¹³C NMR (125 MHz, CDCl₃) 27.1 (C(O)CH₃), 36.2 (C(2)H₂), 42.1 (C(3)H₂), 109.8 (pyrrolylC(4)H), 112.1 (pyrrolylC(3)H), 122.2 (pyrrolyl(2)C(2)H), 127.2 (pyrrolylC(5)H), 128.2 (pyrrolylC(2)), 131.5 (pyrrolyl(2)C(1)H), 172.3 (CO₂H), 197.5 (pyrrolyl(2)C(3)); C₁₁H₁₂NO₃ [M-H]⁻, requires 206.0823, found 206.0823 (0.0 ppm).

1.3.5 Intramolecular Isothiourea-Catalysed Michael Addition-Lactonisation

(4aS,9aR)-3-Phenyl-4a,9a-dihydro-1H,9H-pyrano[4,3-*a*]pyrrolizin-1-one

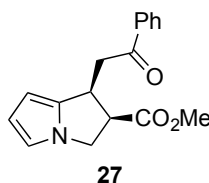


21

Pyrrolyl enone-acid **11** (50.0 mg, 0.19 mmol), *i*-Pr₂NEt (97 μL, 0.56 mmol), pivaloyl chloride (69 μL, 0.56 mmol) in CH₂Cl₂ (2 mL), (+)-BTM **24** (4.7 mg, 0.019 mmol) and *i*-Pr₂NEt (49 μL, 0.28 mmol) gave crude product (>95:5 dr). Purification by column chromatography (EtOAc:petrol ether 10:90) afforded the title compound (>95:5 dr) as a yellow oil (39 mg, 84%); $[\alpha]_D^{20}$ +52.2 (*c* 0.5 CHCl₃); Chiral HPLC analysis; ChiralPak AD-H (90:10 hexane:IPA, flow rate 1.0 mlmin⁻¹, 270 nm, 30 °C) *t*_R 14.3 (major) and *t*_R 16.4 (minor), >99% ee; ν_{\max} (ATR)/cm⁻¹ 3028 (C-H), 1728 (C=O), ¹H NMR (500 MHz, CDCl₃) 3.91 (1H, td, *J* 8.0, 5.0, C(9a)H), 4.27 (1H, dd, *J* 4.6, 4.3, C(4a)H), 4.37 (1H, dd, *J* 10.8, 8.0, C(9)Ha), 4.55 (1H, dd, *J* 10.8, 5.0, C(9)Hb), 5.90 (1H, d, *J* 4.6, C(4)H), 5.95 (1H, dt, *J* 3.3, 1.1, C(5)H), 6.27 (1H, t, *J* 3.1, C(6)H), 6.67 (1H, dd, *J* 2.8, 1.1, C(7)H), 7.36-7.42 (3H, m, C(3)ArC(3,5)H and C(3)ArC(4)H), 7.63-7.66 (2H, m, C(3)ArC(2,6)H); ¹³C NMR (126 MHz, CDCl₃) 35.8 (C(4a)H), 45.2 (C(9a)H), 49.0 (C(9)H^aH^b), 99.6 (C(4)H), 100.0 (C(5)H), 113.8 (C(6)H), 115.2 (C(7)H), 125.2 (C(3)ArC(2,6)H), 128.9 (C(3)ArC(4)), 129.7 (C(3)ArC(3,5)H), 132.4 (C(4b)), 136.6 (C(3)ArC(1)), 148.7 (C(3)), 168.3 (C(1)); HRMS (NSI⁺), C₁₆H₁₃NO₂Na [M+Na]⁺, requires 274.0838, found 274.0843 (+1.8 ppm).

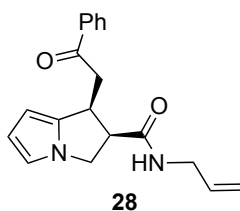
1.3.6 Intramolecular Isothiourea-Catalysed Michael Addition-Lactonisation/Ring Opening

Methyl (1*S*,2*R*)-1-(2-oxo-2-phenylethyl)-2,3-dihydro-1*H*-pyrrolizine-2-carboxylate



Following general procedure E, pyrrolyl enone-acid **11** (50 mg, 0.19 mmol), *i*-Pr₂NEt (97 μ L, 0.56 mmol), pivaloyl chloride (69 μ L, 0.56 mmol) in CH₂Cl₂ (2 mL), (+)-BTM **24** (2.4 mg, 0.0095 mmol) and *i*-Pr₂NEt (49 μ L, 0.28 mmol) gave the crude product (>95:5 dr). Purification by column chromatography (EtOAc:petrol 10:90) gave the title compound (>95:5 dr) as a yellow oil (45 mg, 86%); $[\alpha]_D^{20}$ -54.3 (*c* 1.0 in CHCl₃); Chiral HPLC analysis ChiralPak AD-H (90:10 hexane:IPA, flow rate 1.0 mlmin⁻¹, 220 nm), *t*_R 10.6 (minor) and *t*_R 12.2 (major), >99% ee; ν_{\max} (ATR)/cm⁻¹ 2953 (C-H), 1730 (C=O), 1684 (C=O); ¹H NMR (400 MHz, CDCl₃) 3.19-3.34 (2H, m, pyrrolizine(1)CH^aH^b and pyrrolizine(1)CH^aH^b), 3.58 (3H, s, CO₂CH₃), 4.00 (1H, dd, *J* 16.2, 7.6, pyrrolizine(2)*H*), 4.15 (1H, dd, *J* 11.7, 7.6, pyrrolizine(3)H^aH^b), 4.19-4.26 (1H, m, pyrrolizine(1)*H*), 4.33 (1H, dd, *J* 11.4, 7.2, pyrrolizine(3)H^aH^b), 5.80-5.82 (1H, dt, *J* 3.4, 1.0, pyrrolizine(7)*H*), 6.18-6.22 (1H, m, pyrrolizine(6)*H*), 6.61 (1H, dd, *J* 2.6, 1.2, pyrrolizine(5)*H*), 7.43-7.49 (2H, m, C(O)ArC(3,5)*H*), 7.53-7.58 (1H, m, C(O)ArC(4)*H*), 7.94-7.90 (2H, m, C(O)ArC(2,6)*H*); ¹³C NMR (125 MHz, CDCl₃) 35.3 (pyrrolizineC(1)H), 39.8 (pyrrolizine(1)CH^aH^b), 47.5 (pyrrolizineC(3)H^aH^b), 49.6 (pyrrolizineC(2)H), 51.8 (CO₂CH₃), 99.7 (pyrrolizineC(7)H), 112.3 (pyrrolizineC(6)H), 113.9 (pyrrolizineC(5)H), 127.8 (C(O)ArC(2,6)H), 128.5 (C(O)ArC(3,5)H), 133.1 (C(O)ArC(4)H), 136.7 (pyrrolizineC(7a)), 137.6 (C(O)ArC(1)), 172.1 (CO₂Me), 197.7 (C(O)Ar); HRMS (NSI⁺), C₁₇H₁₈NO₃ [M+H]⁺, requires 284.1281, found 284.1284 (+1.1 ppm).

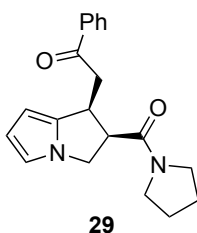
(1*S*,2*R*)-*N*-Allyl-1-(2-oxo-2-phenylethyl)-2,3-dihydro-1*H*-pyrrolizine-2-carboxamide



Following general procedure E, pyrrolyl enone-acid **11** (150 mg, 0.56 mmol), *i*-Pr₂NEt (293 μ L, 1.68 mmol), pivaloyl chloride (207 μ L, 1.68 mmol) in CH₂Cl₂ (5.6 mL), (+)-BTM **24** (7 mg, 0.028 mmol), *i*-Pr₂NEt (293 μ L, 1.68 mmol) and allyl amine (168 μ L, 2.24 mmol) gave, after purification by column chromatography (EtOAc:petrol 15:85) the title compound (>95:5 dr) as a brown oil (140 mg, 81%); $[\alpha]_D^{20}$ -41.0 (*c* 0.5 in CHCl₃); Chiral HPLC analysis: ChiralPak AD-H (80:20 hexane:IPA, 1.0 mlmin⁻¹, 254 nm), *t*_R 9.1 (minor) and *t*_R 11.7 (major), 98.5:1.5 er; ν_{\max} (ATR)/cm⁻¹ 1637(C=O), 1683 (C=O),

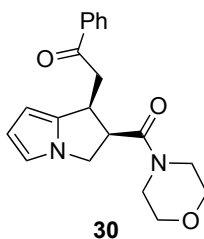
3290 (C-H); ^1H NMR (500 MHz, CDCl_3) 3.33 (1H, dd, J 5.3, pyrrolizine(1) $\text{CH}^a\text{H}^b\text{COAr}$), 3.42 (1H, dd, J 8.6, 18.5, pyrrolizine(1) $\text{CH}^a\text{H}^b\text{COAr}$), 3.59-3.64 (1H, m, $\text{C(O)NHCH}^a\text{H}^b$), 3.72-3.80 (2H, m, pyrrolizine(2) H and $\text{C(O)NHCH}^a\text{H}^b$), 4.09-4.18 (2H, m, pyrrolizine(3) H^aH^b and pyrrolizine(1) H), 4.37 (1H, dd, J 6.0, 10.6, pyrrolizine(3) H^aH^b), 4.96-5.06 (2H, m, $=\text{CH}^a\text{H}^b$ and $=\text{CH}^a\text{H}^b$), 5.61 (1H, ddt, J 6.0, 10.2, 16.3, $\text{CH}=\text{CH}_2$), 5.79-5.80 (2H, m, pyrrolizine(7) H and C(O)NHR), 6.20 (1H, t, J 3.0, pyrrolizine(6) H), 6.61 (1H, br. s, pyrrolizine(5) H), 7.44-7.47 (2H, m, C(O)Ar(3,5)H), 7.55-7.58 (1H, m, C(O)Ar(4)H), 7.93-7.94 (2H, m, C(O)Ar(2,6)H); ^{13}C NMR (125 MHz, CDCl_3) 35.6 (pyrrolizineC(1)H), 40.3 (pyrrolizine(1) $\text{CH}^a\text{H}^b\text{C(O)Ar}$), 42.1 ($\text{C(O)NHCH}^a\text{H}^b$), 48.2 (pyrrolizineC(3) H^aH^b), 51.4 (pyrrolizineC(2)H), 99.4 (pyrrolizineC(7)H), 112.6 (pyrrolizineC(6)H), 114.1 (pyrrolizineC(5)H), 117.1 ($=\text{CH}^a\text{H}^b$), 128.2 (C(O)ArC(2,6)H), 128.7 (C(O)ArC(3,5)H), 133.5 (C(O)ArC(4)H), 133.7 ($\text{CH}=\text{CH}_2$), 136.7 (pyrrolizineC(8)), 138.1 (C(O)ArC(1)), 170.8 (C(O)NHR), 199.4 (C(O)Ar); HRMS (NSI^+), $\text{C}_{20}\text{H}_{21}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$, requires 321.1598, found 321.1589 (-0.1 ppm).

1-Phenyl-2-((1S,2R)-2-(pyrrolidine-1-carbonyl)-2,3-dihydro-1H-pyrrolizin-1-yl)ethan-1-one



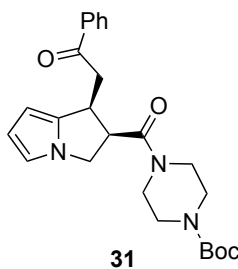
Following general procedure E, pyrrolyl enone-acid **11** (100 mg, 0.37 mmol), $i\text{-Pr}_2\text{NEt}$ (195 μL , 1.12 mmol), pivaloyl chloride (138 μL , 1.12 mmol) in CH_2Cl_2 (3.7 mL), (+)-BTM **24** (4 mg, 0.019 mmol), $i\text{-Pr}_2\text{NEt}$ (65 μL , 0.37 mmol) and pyrrolidine (126 μL , 1.51 mmol) gave, after purification by column chromatography (EtOAc :petrol 15:85) to afford the title compound as a yellow oil (119 mg, quant.); $[\alpha]_D^{20}$ -83.0 (c 1.0 in CHCl_3); Chiral HPLC analysis ChiralPak IB (90:10 hexane:IPA, 1.0 mlmin^{-1} , 211 nm), t_R 13.0 (major) and t_R 15.6 (minor), $>99\%$ ee; ν_{max} (ATR)/ cm^{-1} 1610 ($\text{C}=\text{O}$), 1682 ($\text{C}=\text{O}$), 2951 (C-H); ^1H NMR (500 MHz, CDCl_3) 1.75 (2H, p, J 7.0, C(O)NC(3)H_2), 1.90-2.04 (2H, m, C(O)NC(4)H_2), 2.97-3.04 (2H, m, ArC(O)CH^a and C(O)NC(2)H^a), 3.29-3.36 (1H, m, C(O)NC(2)H^b), 3.46-3.52 (1H, m, C(O)NC(5)H^a), 3.56 (1H, dd, J 9.8, 8.6, ArC(O)CH^b), 3.69-3.74 (1H, m, C(O)NC(5)H^b), 4.01-4.10 (2H, m, C(1) H and C(3) H^a), 4.24-4.29 (1H, m, C(2) H), 4.49-4.56 (1H, m, C(3) H^b), 5.80-5.82 (1H, m, C(7) H), 6.21 (1H, t, J 3.0, C(6) H), 6.62 (1H, dd, J 2.7, 1.3, C(5) H), 7.41-7.45 (2H, m, C(O)ArC(3,5)H), 7.51-7.55 (1H, m, C(O)ArC(4)H), 7.89-7.91 (2H, m, C(O)ArC(2,6)H); ^{13}C NMR (125 MHz, CDCl_3) 24.3 (C(O)NC(3)H_2), 26.1 (C(O)NC(4)H_2), 34.2 (C(2)H), 40.6 ($\text{ArC(O)CH}^a\text{H}^b$), 46.0 ($\text{C(O)NC(2)H}^a\text{H}^b$), 46.7 ($\text{C(O)NC(5)H}^a\text{H}^b$), 48.2 (C(3) H^aH^b), 49.4 (C(1)H), 99.3 (C(7)H), 112.4 (C(6)H), 114.1 (C(5)H), 128.2 (C(O)ArC(2,6)H), 128.7 (C(O)ArC(3,5)H), 133.2 (C(O)ArC(4)H), 136.9 (C(7a)), 138.6 (C(O)ArC(1)), 168.6 (CO_2NR), 198.3 (C(O)Ar); HRMS (NSI^+), $\text{C}_{20}\text{H}_{23}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$, requires 323.1754, found 323.1754 ($+0.0$ ppm).

2-((1*S*,2*R*)-2-(Morpholine-4-carbonyl)-2,3-dihydro-1*H*-pyrrolizin-1-yl)-1-phenylethan-1-one



Following general procedure E, pyrrolyl enone-acid **11** (150 mg, 0.56 mmol), *i*-Pr₂NEt (293 μ L, 1.68 mmol), pivaloyl chloride (207 μ L, 1.68 mmol) in CH₂Cl₂ (5.6 mL), (+)-BTM **24** (7 mg, 0.028 mmol) and *i*-Pr₂NEt (98 μ L, 0.56 mmol) gave, after purification by column chromatography (EtOAc:petrol 10:90) the title compound (>95:5 dr) as a brown oil (29 mg, 66%); $[\alpha]_D^{20}$ -26.2 (*c* 0.5 in CHCl₃); Chiral HPLC analysis: ChiralPak IA (80:20 hexane:IPA, 1.0 mlmin⁻¹, 220 nm), *t*_R 13.3 (major) and *t*_R 16.6 (minor), >99:1 er; ν_{\max} (ATR)/cm⁻¹ 1633 (C=O), 1681 (C=O), 2974, 3064 (C-H); ¹H NMR (500 MHz, CDCl₃) 3.04 (1H, dd, *J* 4.8, 18.1, pyrrolizine(2)*H*), 3.32-3.39 (1H, dd, *J* 6.8, 10.3, pyrrolizine(1)*CH*^a*H*^b), 3.41-3.48 (3H, m, pyrrolizine(1)*CH*^a*H*^b and 2×C(O)NCH^a*H*^b), 3.55-3.59 (2H, m, 2×C(O)NCH^a*H*^b), 3.63-3.73 (2H, 2×C(O)CH₂CH^a*H*^bO), 3.79-3.82 (1H, m, pyrrolizine(1)*H*), 4.07 (1H, dd, *J* 7.4, 10.1, pyrrolizine(3)*H*^a*H*^b), 4.13-4.19 (2H, m, 2×C(O)CH₂CH^a*H*^bO), 4.52-4.55 (1H, m, pyrrolizine(3)*H*^a*H*^b), 5.80 (1H, d, *J* 2.8, pyrrolizine(7)*H*), 6.20 (1H, t, *J* 2.8, pyrrolizine(6)*H*), 6.61 (1H, br. s, pyrrolizine(5)*H*), 7.42-7.45 (2H, m, C(O)Ar(3,5)*H*), 7.53-7.56 (1H, m, C(O)Ar(4)*H*), 7.91 (2H, d, *J* 7.5, C(O)Ar(2,6)*H*); ¹³C NMR (125 MHz, CDCl₃) 34.9 (pyrrolizineC(1)*H*), 40.3 (pyrrolizine(1)*CH*^a*H*^bCOAr), 42.1 (pyrrolizineC(2)*H*), 46.2 (C(O)NC^aH₂), 47.2 (C(O)NC^bH₂), 48.4 (pyrrolizineC(3)*H*^a*H*^b), 66.4 (C(O)NCH₂C^aH₂O), 66.6 (C(O)NCH₂C^bH₂O), 99.5 (pyrrolizineC(7)*H*), 112.4 (pyrrolizineC(6)*H*), 114.2 (pyrrolizineC(5)*H*), 128.2 (C(O)ArC(2,6)*H*), 128.7 (C(O)ArC(3,5)*H*), 133.4 (C(O)ArC(4)*H*), 136.7 (pyrrolizineC(8)), 138.2 (C(O)ArC(1)), 169.0 (C(O)NR), 198.0 (C(O)Ar); HRMS (NSI⁺), C₂₀H₂₂N₂O₃Na [M+H]⁺, requires 361.1523, found 361.1522 (-0.2 ppm).

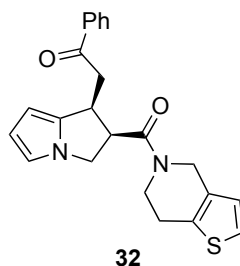
***Tert*-butyl 4-((1*S*,2*R*)-1-(2-oxo-2-phenylethyl)-2,3-dihydro-1*H*-pyrrolizine-2-carbonyl)piperazine-1-carboxylate**



Following general procedure E, pyrrolyl enone-acid **11** (100 mg, 0.37 mmol), *i*-Pr₂NEt (193 μ L, 1.11 mmol), pivaloyl chloride (137 μ L, 1.11 mmol) in CH₂Cl₂ (3 mL), (+)-BTM **24** (4 mg, 0.019 mmol), *i*-

Pr₂NEt (293 μ L, 1.68 mmol) and *N*-Boc piperazine (276 mg, 1.48 mmol) gave, after purification by column chromatography (EtOAc:petrol 20:80) the title compound (>95:5 dr) as a brown oil (121 mg, 75%); $[\alpha]_D^{20}$ -31.6 (*c* 0.5 in CHCl₃); Chiral HPLC analysis: ChiralPak AD-H (90:10 hexane:IPA, 1.0 mlmin⁻¹, 211 nm), *t_R* 23.0 (major) and *t_R* 30.3 (minor), >99:1 er; ν_{\max} (ATR)/cm⁻¹ 1163, 1633 (C=O), 1681 (C=O), 2927, 2974 (C-H); ¹H NMR (300 MHz, CDCl₃) 1.47 (9H, s, C(CH₃)₃), 2.99-3.06 (1H, m, pyrrolizine(2)*H*), 3.25-3.31 (3H, m, pyrrolizine(1)*CH*^a*H*^bCOAr and BocNCH₂), 3.40-3.70 (6H, m, 2×NCH₂ and BocNCH₂), 4.04-4.20 (3H, m, pyrrolizine(3)*H*^a*H*^b and pyrrolizine(1)*H* and pyrrolizine(1)*CH*^a*H*^bCOAr), 4.50-4.56 (1H, m, pyrrolizine(3)*H*^a*H*^b); ¹³C NMR (75 MHz, CDCl₃) 28.5 (C(CH₃)₃), 35.0 (pyrrolizineC(1)*H*), 40.4 (pyrrolizineC(2)*H*), 41.6 (NCH₂), 45.7 (BocNCH₂), 47.5 (pyrrolizine(1)*CH*^a*H*^bCOAr), 48.4 (pyrrolizineC(3)*H*₂), 80.4 (C(CH₃)₃), 99.5 (pyrrolizineC(7)*H*), 112.4 (pyrrolizineC(6)*H*), 114.3 (pyrrolizineC(5)*H*), 128.2 (C(O)ArC(2,6)*H*), 128.2 (C(O)ArC(3,5)*H*), 133.4 (C(O)ArC(4)*H*), 136.8 (pyrrolizineC(7a)), 138.2 (C(O)ArC(1)), 154.6 (NC(O)C(CH₃)₃), 168.9 (CO₂Me), 198.1 (C(O)Ar); HRMS (NSI⁺), C₂₅H₃₂N₃O₄ [M+CH₂+H]⁺, requires 438.2387, found 438.2394 (1.5 ppm).

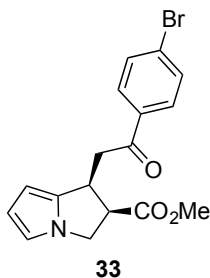
1-Phenyl-2-((1*S*,2*R*)-2-(4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-6-carbonyl)-2,3-dihydro-1*H*-pyrrolizin-1-yl)ethan-1-one



Following general procedure E, pyrrolyl enone-acid **11** (100 mg, 0.37 mmol), *i*-Pr₂NEt (193 μ L, 1.11 mmol), pivaloyl chloride (137 μ L, 1.11 mmol) in CH₂Cl₂ (3 mL), (+)-BTM **24** (4 mg, 0.019 mmol), *i*-Pr₂NEt (293 μ L, 1.68 mmol) and 4,5,6,7-tetrahydrothieno[3,2-*c*] pyridine (260 mg, 1.48 mmol) gave, after purification by column chromatography (EtOAc:petrol 15:85) the title compound (90:10 dr, 50:50 rotameric mixture) as a brown oil (87 mg, 60%); $[\alpha]_D^{20}$ -50.6 (*c* 0.5 in CHCl₃); Chiral HPLC analysis: ChiralPak AD-H (90:10 hexane:IPA, 1.0 mlmin⁻¹, 220 nm), *t_R* 35.3 (major) and *t_R* 46.5 (minor), >99:1 er; ν_{\max} (ATR)/cm⁻¹ 1660 (C=O), 1734 (C=O), 2951, 3089 (C-H); data for single rotamer; ¹H NMR (500 MHz, CDCl₃) 2.64 (1H, dt, *J* 5.2, 16.0, *CH*), 2.95-2.99 (1H, m, *CH*), 3.03-3.12 (2H, m, 2×*CH*), 3.57 (1H, ddd, *J* 4.7, 7.4, 12.6, *CH*), 3.90 (1H, dt, *J* 5.1, 12.8, *CH*), 4.05-4.13 (4H, m, 4×*CH*), 4.57-4.64 (2H, m, 4×*CH*), 5.83-5.85 (1H, m, pyrrolizine(7)*H*), 6.22 (1H, t, *J* 3.0, pyrrolizine(6)*H*), 6.64-6.65 (1H, m, pyrrolizine(5)*H*), 6.74 (1H, d, *J* 5.2, thienyl(3)*H*), 7.14 (1H, d, *J* 5.2, thienyl(2)*H*), 7.40-7.44 (2H, m, Ar(3,5)*H*), 7.51-7.56 (1H, m, Ar(4)*H*), 7.82-7.83 (2H, m, Ar(2,6)*H*); ¹³C NMR (125 MHz, CDCl₃) 24.7 (*CH*), 34.9 (*CH*), 40.2 (*CH*), 43.0 (*CH*), 46.0 (*CH*),

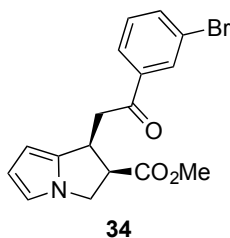
48.1 (CH), 48.4 (CH), 99.6 (pyrrolizineC(7)H), 112.4 (pyrrolizineC(6)H), 114.2 (pyrrolizineC(5)H), 123.7 (thienylC(2)H), 124.7 (thienylC(3)H), 128.1 (ArCH), 128.7 (ArCH), 132.4 (ArC), 133.3 (ArC), 134.3 (ArCH), 136.7 (ArC), 138.3 (ArC), 169.1 (C(O)NR), 197.9 (C(O)Ar); HRMS (NSI⁺), C₂₂H₂₁N₂O₂S [M+H]⁺, requires 377.1318, found 377.1295 (−6.1 ppm).

Methyl (1*S*,2*R*)-1-(2-(4-bromophenyl)-2-oxoethyl)-2,3-dihydro-1*H*-pyrrolizine-2-carboxylate



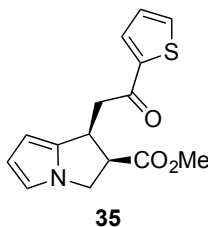
Following general procedure E pyrrolyl enone-acid **12** (60 mg, 0.17 mmol), *i*-Pr₂NEt (90 μL, 0.52 mmol), pivaloyl chloride (64 μL, 0.52 mmol) in CH₂Cl₂ (2 mL), (+)-BTM **24** (2.2 mg, 0.009 mmol) and *i*-Pr₂NEt (45 μL, 0.24 mmol) gave the crude product (>95:5 dr). Purification by column chromatography (EtOAc:petrol 10:90) gave the title compound (>95:5 dr) as a yellow oil (49 mg, 78%); [α]_D²⁰ −50.8 (*c* 0.5 in CHCl₃); Chiral HPLC analysis: ChiralPak AD-H (90:10 hexane:IPA, 1.0 mlmin^{−1}, 254 nm), *t*_R 14.5 (minor) and *t*_R 17.4 (major), >99% ee; ν_{max} (ATR)/cm^{−1} 1689 (C=O), 1732 (C=O), 2889, 2951 (C-H); ¹H NMR (400 MHz, CDCl₃) 3.14-3.30 (2H, m, pyrrolizine(1)CH^aH^bC(O)Ar and pyrrolizine(1)CH^aH^bC(O)Ar), 3.59 (3H, s, CO₂CH₃), 3.98 (1H, dd, *J* 8.1, 7.8, pyrrolizine(2)*H*), 4.12-4.23 (2H, m, pyrrolizine(3)H^aH^b and pyrrolizine(1)*H*), 4.32 (1H, dd, *J* 10.7, 7.4, pyrrolizine(3)H^aH^b), 5.78-5.81 (1H, m, pyrrolizine(7)*H*), 6.19 (1H, t, *J* 3.0, pyrrolizine(6)*H*), 6.60 (1H, dd, *J* 2.8, 1.2, pyrrolizine(5)*H*), 6.57-6.61 (2H, m, C(O)ArC(3,5)*H*), 7.76-7.81 (2H, m, C(O)ArC(2,6)*H*); ¹³C NMR (125 MHz, CDCl₃) 35.7 (pyrrolizineC(1)H), 40.3 (pyrrolizine(1)CH^aH^bC(O)Ar), 48.0 (pyrrolizineC(3)H^aH^b), 50.0 (pyrrolizineC(2)H), 52.4 (CO₂CH₃), 100.3 (pyrrolizineC(7)H), 112.8 (pyrrolizineC(6)H), 114.2 (pyrrolizineC(5)H), 128.7 (C(O)ArC(4)), 129.9 (C(O)ArC(2,6)H), 132.3 (C(O)ArC(3,5)H), 135.9 (pyrrolizineC(7a)), 137.9 (C(O)ArC(1)), 172.47 (CO₂Me), 197.2 (C(O)Ar); HRMS (NSI⁺), C₁₇H₁₇⁷⁷BrNO₄ [M+H]⁺, requires 362.0386, found 362.0378 (−2.3 ppm).

Methyl (1*S*,2*R*)-1-(2-(3-bromophenyl)-2-oxoethyl)-2,3-dihydro-1*H*-pyrrolizine-2-carboxylate



Following general procedure E, pyrrolyl enone-acid **13** (100 mg, 0.29 mmol), *i*-Pr₂NEt (151 μ L, 0.87 mmol), pivaloyl chloride (107 μ L, 0.87 mmol) in CH₂Cl₂ (2 mL), (+)-BTM **24** (4 mg, 0.016 mmol) and *i*-Pr₂NEt (76 μ L, 0.44 mmol) gave the crude product (>95:5 dr). Purification by column chromatography (EtOAc:petrol 10:90) gave the title compound (>95:5 dr) as a brown oil (84 mg, 80%); $[\alpha]_D^{20}$ -53.4 (*c* 0.5 in CHCl₃); Chiral HPLC analysis: ChiralPak OD-H (90:10 hexane:IPA, 1.0 mlmin⁻¹, 220 nm), *t*_R 15.6 (minor) and *t*_R 17.6 (major), >99% ee; ν_{\max} (ATR)/cm⁻¹ 1695 (C=O), 1771 (C=O), 2980 (C-H); ¹H NMR (500 MHz, CDCl₃) 3.19 (1H, dd, *J* 6.6, 17.8, pyrrolizine(1)*CH*^aCOAr), 3.28 (1H, dd, *J* 7.6, 17.8, pyrrolizine(1)*CH*^bCOAr), 3.61 (3H, s, CO₂CH₃), 3.99 (1H, q, *J* 7.8, pyrrolizine(2)*H*), 4.14-4.21 (2H, m, pyrrolizine(3)*H*^a and pyrrolizine(1)*H*), 4.32 (1H, dd, *J* 7.4, 10.6, pyrrolizine(3)*H*^b), 5.80 (1H, d, *J* 3.4, pyrrolizine(7)*H*), 6.19 (1H, t, *J* 3.0, pyrrolizine(6)*H*), 6.61 (1H, dd, *J* 1.2, 2.6, pyrrolizine(5)*H*), 7.33 (1H, t, *J* 7.8, C(O)Ar(5)*H*), 7.68 (1H, ddd, 0.9, 1.8, 7.9, C(O)Ar(4)*H*), 7.83 (1H, dt, *J* 1.1, 7.8, C(O)Ar(6)*H*), 8.04 (1H, t, *J* 1.7, C(O)Ar(2)*H*); ¹³C NMR (125 MHz, CDCl₃) 35.4 (pyrrolizineC(1)*H*), 40.2 (pyrrolizine(1)*CH*^a*H*^bCOAr), 47.8 (pyrrolizineC(3)*H*^a*H*^b), 49.8 (pyrrolizineC(2)*H*), 52.2 (CO₂CH₃), 100.1 (pyrrolizineC(7)*H*), 112.6 (pyrrolizineC(6)*H*), 114.2 (pyrrolizineC(5)*H*), 123.2 (C(O)ArC(3)), 126.6 (C(O)ArC(6)*H*), 130.4 (C(O)ArC(5)*H*), 131.2 (C(O)ArC(2)), 136.2 (C(O)ArC(4)*H*), 137.6 (pyrrolizineC(8)), 138.6 (C(O)ArC(1)), 172.2 (CO₂Me), 196.7 (C(O)Ar); HRMS (NSI⁺), C₁₇H₁₇Br⁷⁹NO₃ [M+H]⁺, requires 362.0386, found 362.0386 (-0.1 ppm).

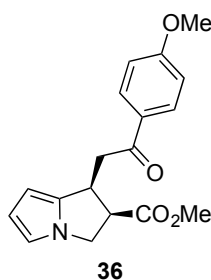
Methyl (1*S*,2*R*)-1-(2-oxo-2-(thiophen-2-yl)ethyl)-2,3-dihydro-1*H*-pyrrolizine-2-carboxylate



Following general procedure E, pyrrolyl enone-acid **14** (100 mg, 0.29 mmol), *i*-Pr₂NEt (151 μ L, 0.87 mmol), pivaloyl chloride (107 μ L, 0.87 mmol) in CH₂Cl₂ (2 mL), (+)-BTM **24** (4 mg, 0.016 mmol) and *i*-Pr₂NEt (76 μ L, 0.44 mmol) gave, after purification by column chromatography (EtOAc:petrol ether 10:90) the title compound (>95:5 dr) as a brown oil (84 mg, 80%); $[\alpha]_D^{20}$ -75.2 (*c* 0.5 in CHCl₃); Chiral HPLC analysis: ChiralPak OD-H (90:10 hexane:IPA, 1.0 mlmin⁻¹, 270 nm), *t*_R 18.3 (minor) and *t*_R 30.9 (major), 99:1 er; ν_{\max} (ATR)/cm⁻¹ 1661 (C=O), 1724 (C=O), 2895, 2951 (C-H); ¹H NMR (400 MHz, CDCl₃) 3.20 (2H, dq, *J* 7.2, 17.2, pyrrolizine(1)*CH*^a*H*^b), 3.60 (3H, s, CO₂CH₃), 3.97 (1H, q, *J* 7.8, pyrrolizine(2)*H*), 4.14 (1H, dd, *J* 7.8, 10.7, pyrrolizine(3)*H*^a), 4.20 (1H, q, *J* 7.5, pyrrolizine(1)*H*), 4.33 (1H, dd, *J* 7.3, 10.7, pyrrolizine(3)*H*^b), 5.80 (1H, d, *J* 3.4, pyrrolizine(7)*H*), 6.19 (1H, t, *J* 3.0, pyrrolizine(6)*H*), 6.60 (1H, dd, *J* 1.2, 2.6, pyrrolizine(5)*H*), 7.11 (1H, dd, *J* 3.9, 4.9, C(O)thienyl(4)*H*), 7.62-7.65 (2H, m, C(O)thienyl(3)*H* and C(O)thienyl(5)*H*); ¹³C NMR (100 MHz,

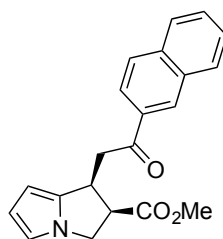
CDCl₃) 35.5 (pyrrolizineC(1)H), 40.7 (pyrrolizine(1)CH^aH^bCO), 47.7 (pyrrolizineC(3)H^aH^b), 49.8 (pyrrolizineC(2)H), 52.1 (CO₂CH₃), 100.0 (pyrrolizineC(7)H), 112.6 (pyrrolizineC(6)H), 114.2 (pyrrolizineC(5)H), 128.3 (C(O)thienylC(4)H), 132.1 (C(O)thienylC(3)H), 133.8 (C(O)thienylC(5)H), 137.6 (pyrrolizineC(8)), 144.2 (C(O)thienylC(2)), 172.2 (CO₂Me), 190.7 (C(O)thienyl); HRMS (NSI⁺), C₁₅H₁₅NO₃SNa [M+Na]⁺, requires 312.0665, found 312.0660 (−1.6 ppm).

Methyl (1*S*,2*R*)-1-(2-(4-methoxyphenyl)-2-oxoethyl)-2,3-dihydro-1*H*-pyrrolizine-2-carboxylate



Following general procedure E, pyrrolyl enone-acid **15** (42 mg, 0.13 mmol), *i*-Pr₂NEt (70 μL, 0.40 mmol), pivaloyl chloride (50 μL, 0.40 mmol) in CH₂Cl₂ (2 mL), (+)-BTM **24** (1.7 mg, 0.007 mmol) and *i*-Pr₂NEt (35 μL, 0.20 mmol) gave the crude product (>95:5 dr). Purification by column chromatography (EtOAc:petrol 10:90) gave the title compound (>95:5 dr) as a yellow oil (41 mg, 98%; %); [α]_D²⁰ −61.3 (*c* 0.5 in CHCl₃); Chiral HPLC analysis: ChiralPak AD-H (90:10 hexane:IPA, flow rate 1.0 mlmin^{−1}, 270 nm) t_R 20.0 (minor) and t_R 25.1 (major) >99:1 er; ν_{max} (ATR)/cm^{−1} 2953 (C-H), 1734 (C=O), 1676 (C=O); ¹H NMR (500 MHz, CDCl₃) 3.12-3.29 (2H, m, pyrrolizine(1)CH^aH^bC(O)Ar and pyrrolizine(1)CH^aH^bC(O)Ar), 3.57 (3H, s, CO₂CH₃), 3.86 (3H, s, C(O)Ar(4)OCH₃), 3.94-4.02 (1H, m, pyrrolizine(2)H), 4.11-4.25 (2H, m, pyrrolizine(3)H^aH^b and pyrrolizine(1)H), 4.33 (1H, dd, *J* 7.1, 10.6, pyrrolizine(3)H^aH^b), 5.80 (1H, dt, *J* 1.0, 3.4, pyrrolizine(7)H), 6.19 (1H, m, pyrrolizine(6)H), 6.60 (1H, dd, *J* 1.3, 2.6, pyrrolizine(5)H), 6.92 (2H, d, *J* 8.9, C(O)ArC(3,5)H), 7.90 (2H, d, *J* 9.0, C(O)ArC(2,6)H); ¹³C NMR (125 MHz, CDCl₃) 35.7 (pyrrolizineC(1)H), 39.7 (pyrrolizine(1)CH^aH^b), 47.8 (pyrrolizineC(3)H^aH^b), 49.9 (pyrrolizineC(2)H), 52.1 (CO₂CH₃), 55.6 (C(O)Ar(4)OCH₃), 99.9 (pyrrolizineC(7)H), 112.5 (pyrrolizineC(6)H), 113.8 (C(O)ArC(2,6)H), 114.0 (pyrrolizineC(5)H), 130.1 (C(O)ArC(1)), 130.4 (C(O)ArC(3,5)H), 138.0 (C(O)ArC(4)), 163.6 (pyrrolizineC(7a)), 172.3 (CO₂Me), 196.4 (C(O)Ar); HRMS (NSI⁺), C₁₈H₂₀NO₄ [M+H]⁺, requires 314.1389, found 314.1388 (+0.3 ppm).

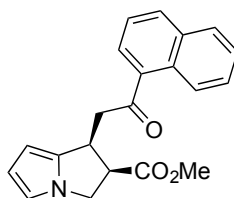
Methyl (1*S*,2*R*)-1-(2-(naphthalen-2-yl)-2-oxoethyl)-2,3-dihydro-1*H*-pyrrolizine-2-carboxylate



37

Following general procedure E, pyrrolyl enone-acid **16** (100 mg, 0.31 mmol), *i*-Pr₂NEt (162 μL, 0.93 mmol), pivaloyl chloride (115 μL, 0.93 mmol) in CH₂Cl₂ (3 mL), (+)-BTM **24** (4 mg, 0.016 mmol) and *i*-Pr₂NEt (82 μL, 0.47 mmol) gave the crude product (>95:5 dr). Purification by column chromatography (EtOAc:petrol 10:90) gave the title compound (>95:5 dr) as a white solid (84 mg, 81%); mp 108-110 °C; $[\alpha]_D^{20}$ -64.1 (*c* 0.5 in CHCl₃); Chiral HPLC analysis ChiralPak OD-H (90:10 hexane:IPA, flow rate 1.0 mlmin⁻¹, 220 nm, 30 °C), *t*_R 19.3 (minor) and *t*_R 26.5 (major), >99:1 er; *v*_{max} (ATR)/cm⁻¹ 1674 (C=O), 1720 (C=O), 3021 (C-H); ¹H NMR (400 MHz, CDCl₃) 3.35 (1H, dd, *J* 7.8, 17.6, pyrrolizine(1)CH^aH^bC(O)Ar), 3.46 (1H, dd, *J* 7.8, 17.6, pyrrolizine(1)CH^aH^bC(O)Ar), 3.58 (3H, s, CO₂CH₃), 4.03 (1H, q, *J* pyrrolizine(2)*H*), 4.18 (1H, dd, *J* 7.8, 10.5, pyrrolizine(3)H^aH^b), 4.29 (1H, q, *J* 7.3, pyrrolizine(1)*H*), 4.37 (1H, dd, *J* 7.2, 10.5, pyrrolizine(3)H^aH^b), 5.85 (1H, br. s, pyrrolizine(7)*H*), 6.21 (1H, br. s, pyrrolizine(6)*H*), 6.63 (1H, br. s, pyrrolizine(5)*H*), 7.54-7.62 (2H, m, Ar*H*), 7.86-8.03 (4H, m, Ar*H*), 8.42 (1H, br. s, Ar*H*); ¹³C NMR (125 MHz, CDCl₃) 35.7 (pyrrolizineC(1)H), 40.2 (pyrrolizine(2)CH^aH^bC(O)Ar), 47.8 (pyrrolizineC(3)H^aH^b), 49.9 (pyrrolizineC(2)H), 51.8 (CO₂CH₃), 100.0 (pyrrolizineC(7)H), 112.6 (pyrrolizineC(6)H), 114.1 (pyrrolizineC(5)H), 123.8 (ArCH), 127.0 (ArCH), 127.9 (ArCH), 128.6 (ArCH), 128.6 (ArCH), 129.7 (ArCH), 129.8 (ArCH), 132.6 (ArC), 134.2 (ArC), 135.8 (pyrrolizineC(7a)), 137.9 (C(O)ArC(1)), 172.4 (CO₂Me), 197.9 (C(O)Ar); HRMS (NSI⁺), C₂₁H₁₉NO₃Na [M+Na]⁺, requires 356.1257, found 356.1250 (-1.1 ppm).

Methyl (1*S*,2*R*)-1-(2-(naphthalen-1-yl)-2-oxoethyl)-2,3-dihydro-1*H*-pyrrolizine-2-carboxylate

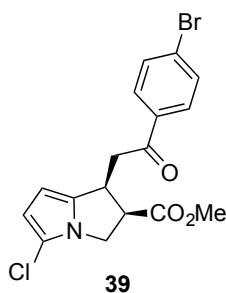


38

Following general procedure E, pyrrolyl enone-acid **17** (100 mg, 0.31 mmol), *i*-Pr₂NEt (162 μL, 0.93 mmol), pivaloyl chloride (115 μL, 0.93 mmol) in CH₂Cl₂ (3 mL), (+)-BTM **24** (4 mg, 0.016 mmol) and *i*-Pr₂NEt (82 μL, 0.47 mmol) gave the crude product (>95:5 dr). Purification by column chromatography (EtOAc:petrol 10:90) gave the title compound (>95:5 dr) as a white solid (74 mg,

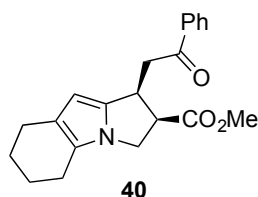
72%); $[\alpha]_D^{20}$ -55.2 (*c* 0.5 in CHCl₃); Chiral HPLC analysis ChiralPak AD-H (90:10 hexane:IPA, flow rate 1.0 mlmin⁻¹, 211 nm, 30 °C), *t*_R 12.5 (minor) and *t*_R 14.2 (major), >99:1 er; *v*_{max} (ATR)/cm⁻¹ 1165, 1670 (C=O), 1732 (C=O), 2951 (C-H); ¹H NMR (400 MHz, CDCl₃) 3.36 (2H, d, *J* 7.2, pyrrolizine(1)CH^aH^bC(O)Ar and pyrrolizine(1)CH^aH^bC(O)Ar), 3.57 (3H, s, CO₂CH₃), 4.05 (1H, q, *J* pyrrolizine(2)*H*), 4.18 (1H, dd, *J* 7.8, 10.6, pyrrolizine(3)H^aH^b), 4.30 (1H, q, *J* 7.5, pyrrolizine(1)*H*), 4.35 (1H, dd, *J* 7.1, 10.6, pyrrolizine(3)H^aH^b), 5.86 (1H, d, *J* 3.4, pyrrolizine(7)*H*), 6.20 (1H, *J* 3.0, pyrrolizine(6)*H*), 6.62 (1H, dd, *J* 1.2, 2.5, pyrrolizine(5)*H*), 7.46-7.49 (1H, m, Ar*H*), 7.52-7.56 (1H, m, Ar*H*), 7.61 (1H, ddd, *J* 1.3, 6.9, 8.5, Ar*H*), 7.81-7.83 (1H, m, Ar*H*), 7.87-7.88 (1H, m, Ar*H*), 7.98 (1H, br. d, *J* 8.2, Ar*H*), 8.61 (1H, br. d, *J* 8.6, Ar*H*); HRMS (NSI⁺), C₁₁H₁₂NO₃ [M+H]⁺, requires 206.0823, found 206.0823 (0.0 ppm).

Methyl (1*S*,2*R*)-1-(2-(4-bromophenyl)-2-oxoethyl)-5-chloro-2,3-dihydro-1*H*-pyrrolizine-2-carboxylate



Following general procedure E, pyrrolyl enone-acid **19** (40 mg, 0.11 mmol), *i*-Pr₂NEt (55 μL, 0.32 mmol), pivaloyl chloride (39 μL, 0.32 mmol) in CH₂Cl₂ (1 mL), (+)-BTM **24** (1 mg, 0.005 mmol) and *i*-Pr₂NEt (18 μL, 0.11 mmol) gave, after purification by column chromatography (EtOAc:petrol 10:90) the title compound (94:6 dr) as a brown oil (29 mg, 66%); $[\alpha]_D^{20}$ -40.1 (*c* 0.5 in CHCl₃); Chiral HPLC analysis: ChiralPak OD-H (90:10 hexane:IPA, 1.0 mlmin⁻¹, 211 nm), *t*_R 18.0 (minor) and *t*_R 21.4 (major), >99:1 er; *v*_{max} (ATR)/cm⁻¹ 1584 (C=O), 1688 (C=O), 2926, 2951 (C-H); ¹H NMR (500 MHz, CDCl₃) 3.18 (1H, dd, *J* 7.1, 17.7, pyrrolizine(1)CH^aH^bCOAr), 3.24 (1H, dd, *J* 7.2, 17.7, pyrrolizine(1)CH^aH^bCOAr), 3.62 (3H, s, CO₂CH₃), 3.97 (1H, q, *J* 7.8, pyrrolizine(2)*H*), 4.12 (1H, dd, *J* 7.9, 10.9, pyrrolizine(3)H^aH^b), 4.17-4.27 (2H, m, pyrrolizine(1)*H* and pyrrolizine(3)H^aH^b), 5.74 (1H, dd, *J* 0.8, 3.6, pyrrolizine(7)*H*), 5.97 (1H, d, *J* 3.6, pyrrolizine(6)*H*), 7.60 (2H, d, *J* 8.6, C(O)Ar(3,5)*H*), 7.77 (1H, d, *J* 8.6, C(O)Ar(2,6)*H*); ¹³C NMR (125 MHz, CDCl₃) 36.4 (pyrrolizineC(1)*H*), 39.9 (pyrrolizine(1)CH^aH^bCOAr), 46.4 (pyrrolizineC(3)H^aH^b), 49.3 (pyrrolizineC(2)*H*), 52.3 (CO₂CH₃), 100.9 (pyrrolizineC(7)*H*), 109.6 (pyrrolizineC(6)*H*), 127.5 (C(O)ArC(4)Br), 128.7 (pyrrolizineC(8)), 129.6 (C(O)ArC(3,5)*H*), 132.1 (C(O)ArC(2,6)*H*), 135.5 (C(O)ArC(1)), 136.4 (pyrrolizineC(5)Cl), 171.8 (CO₂Me), 196.8 (C(O)Ar); HRMS (NSI⁺), C₁₇H₁₆Br⁷⁹ClNO₃ [M+Na]⁺, requires 397.9974, found 397.9974 (0.0 ppm).

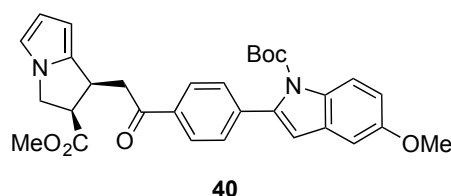
Methyl (1*S*,2*R*)-1-(2-oxo-2-phenylethyl)-2,3,5,6,7,8-hexahydro-1*H*-pyrrolo[1,2-*a*]indole-2-carboxylate



Following general procedure E, pyrrolyl enone-acid **18** (100 mg, 0.31 mmol), *i*-Pr₂NEt (162 μ L, 0.93 mmol), pivaloyl chloride (115 μ L, 0.93 mmol) in CH₂Cl₂ (3 mL), (+)-BTM **24** (4 mg, 0.016 mmol) and *i*-Pr₂NEt (54 μ L, 0.31 mmol) gave, after purification by column chromatography (EtOAc:petrol 10:90) the title compound (>95:5 dr) as a brown oil (55 mg, 53%); $[\alpha]_D^{20}$ – 33.1 (*c* 0.5 in CHCl₃); Chiral HPLC analysis: ChiralPak IC (90:10 hexane:IPA, 1.0 mlmin^{–1}, 211 nm), *t*_R 14.7 (major) and *t*_R 17.4 (minor), >99% ee; ν_{max} (ATR)/cm^{–1} 1665 (C=O), 1730 (C=O), 2841, 2927, 2953 (C–H); ¹H NMR (500 MHz, CDCl₃) 1.68–1.74 (2H, m, pyrroloindolyl(7)*H*₂), 1.76–1.84 (2H, m, pyrroloindolyl(6)*H*₂), 2.47–2.55 (4H, m, pyrroloindolyl(8)*H*₂ and pyrroloindolyl(5)*H*₂), 3.18 (1H, dd, *J* 6.5, 17.8, pyrroloindolyl(1)CH^aH^bCOAr), 3.57 (3H, s, CO₂CH₃), 3.92–4.01 (2H, m, pyrroloindolyl(2)*H* and pyrroloindolyl(3)*H*^c), 4.14 (1H, dd, *J* 7.0, 9.9, pyrroloindolyl(3)*H*^b), 4.19 (1H, q, *J* 7.4, pyrroloindolyl(1)*H*), 5.59 (1H, s, pyrroloindolyl(9)*H*), 7.43–7.46 (2H, m, C(O)Ar(3,5)*H*), 7.53–7.57 (1H, m, C(O)Ar(4)*H*), 7.91–7.93 (C(O)Ar(2,6)*H*); ¹³C NMR (125 MHz, CDCl₃) 21.9 (pyrroloindolylC(9)*H*₂), 23.4 (pyrroloindolylC(8)*H*₂), 23.7 (pyrroloindolylC(5)*H*₂), 23.8 (pyrroloindolylC(6)*H*₂), 35.6 (pyrroloindolylC(1)*H*), 40.5 (pyrroloindolyl(1)CH^aH^bCOAr), 45.4 (pyrroloindolylC(3)*H*^aH^b), 49.6 (pyrroloindolylC(2)*H*), 52.1 (CO₂CH₃), 98.4 (pyrroloindolylC(9)*H*), 121.3 (pyrroloindolylC(8a)), 122.9 (pyrroloindolylC(4a)), 128.1 (C(O)ArC(3,5)*H*), 128.7 (C(O)ArC(2,6)*H*), 133.3 (C(O)ArC(4)*H*), 135.5 (pyrroloindolylC(9a)), 137.0 (C(O)ArC(1)), 172.5 (CO₂Me), 198.1 (C(O)Ar); In our hands this compound proved to be unstable to mass spectrometry analysis.

1.3.7 Derivatisations

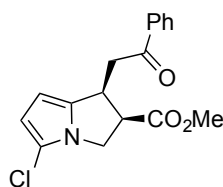
***Tert*-butyl 5-methoxy-2-(4-(2-((1*S*,2*R*)-2-(methoxycarbonyl)-2,3-dihydro-1*H*-pyrrolizin-1-yl)acetyl)phenyl)-1*H*-indole-1-carboxylate**



A flame-dried schlenk flask, under inert atmosphere, was charged with Pd(PPh₃)₄ (16 mg, 0.014 mmol), pyrrolizine **33** (50 mg, 0.14), Na₂CO₃ (45 mg, 0.42 mmol) and *N*-Boc-5-methoxy-2-indolylboronic acid (49 mg, 0.17 mmol). Degassed DME (2.2 mL) was added and reaction stirred at

80 °C for 16 h. Reaction cooled to rt and dilute with EtOAc, washed with brine (×3), dried over MgSO₄ and concentrated under reduced pressure to give crude reaction mixture that, following column chromatography (EtOAc:Petrol 20:80), gave the title compound (>95:5 dr) as a brown oil (45 mg, 60%); $[\alpha]_D^{20}$ -22.0 (c 0.5 in CHCl₃); Chiral HPLC analysis ChiralPak AD-H (90:10 hexane:IPA, 1.0 mlmin⁻¹, 254 nm), t_R 42.6 (major) and t_R 52.0 (minor), >99:1 er; ν_{max} (ATR)/cm⁻¹ 1607, 1681 (C=O), 1726 (C=O), 2929, 2951 (C-H); ¹H NMR (300 MHz, CDCl₃) 1.35 (9H, s, NCO₂C(CH₃)₃), 3.20-3.38 (2H, m, pyrrolizine(1)CH^aH^bC(O)indole), 3.62 (3H, s, CO₂CH₃), 3.87 (3H, s, ArOCH₃), 3.97-4.05 (1H, m, pyrrolizine(2)H), 4.14-4.27 (2H, m, pyrrolizine(1)H and pyrrolizine(3)H^aH^b), 4.35 (1H, dd, J 7.2, 10.6, pyrrolizine(3)H^aH^b), 5.81 (1H, d, J 3.3, pyrrolizine(7)H), 6.19-6.21 (1H, m, pyrrolizine(6)H), 6.55 (1H, s, indolyl(3)H), 6.61 (1H, dd, J 1.2, 2.6, pyrrolizine(5)H), 6.95-7.03 (2H, m, indolyl(6)H and indolyl(7)H), 7.50 (2H, d, J 8.4, C(O)Ar(3,5)H), 7.95 (2H, d, J 8.5, C(O)Ar(2,6)H), 8.08 (1H, d, J 9.0, indolyl(4)H); ¹³C NMR (100 MHz, CDCl₃) 27.9 (C(CH₃)₃), 35.6 (pyrrolizineC(1)H), 40.2 (pyrrolizine(1)CH^aH^bC(O)Ar), 47.8 (pyrrolizineC(3)H^aH^b), 49.9 (pyrrolizineC(2)H), 52.1 (CO₂CH₃), 55.9 (ArOCH₃), 84.0 (NCO₂C(CH₃)₃), 100.1 (pyrrolizineC(7)H), 103.2 (indolylC(3)H), 111.2 (pyrrolizineC(7)H), 112.2 (pyrrolizineC(6)H), 113.9 (indolylC(4)H), 114.1 (indolylC(6)H), 116.3 (pyrrolizineC(5)H), 127.7 (C(O)ArC(3,5)H), 128.9 (C(O)Ar(2,6)H), 130.0 (indolylC(2)), 132.6 (indolylC(7a)), 135.8 (indolylC(3a)), 137.9 (pyrrolizineC(8)), 139.8 (C(O)ArC(1)), 140.0 (C(O)ArC(4)), 150.1 (NCO₂*t*-Bu), 156.3 (indolylC(5)), 172.3 (CO₂Me), 197.5 (C(O)Ar); HRMS (NSI⁺), C₃₁H₃₂N₂O₆Na [M+Na]⁺, requires 551.2158, found 551.2138 (-3.6 ppm).

Methyl (1*S*,2*R*)-5-chloro-1-(2-oxo-2-phenylethyl)-2,3-dihydro-1*H*-pyrrolizine-2-carboxylate



41

To a solution of pyrrolizine **27** in CH₂Cl₂ (5 mL) at 0 °C, under inert atmosphere was added *N*-chlorosuccinimide (47 mg, 0.35 mmol) and reaction stirred for 2 h. Reaction was dilute with CH₂Cl₂ (5 mL), washed with Na₂CO₃ (×3), dried over MgSO₄ and concentrated under reduced pressure to give crude reaction mixture that, following column chromatography (EtOAc:Petrol 20:80), gave the title compound (>95:5 dr) as a brown oil (86 mg, 79%); $[\alpha]_D^{20}$ -31.2 (c 0.5 in CHCl₃); Chiral HPLC analysis ChiralPak OD-H (90:10 hexane:IPA, 1.0 mlmin⁻¹, 211 nm), t_R 24.2 (minor) and t_R 39.7 (major), >99:1 er. ν_{max} (ATR)/cm⁻¹ 1681 (C=O), 1730 (C=O), 3001 (C-H); ¹H NMR (500 MHz, CDCl₃) 3.18-3.30 (2H, m, pyrrolizine(1)CH^aH^bC(O)Ar and pyrrolizine(1)CH^aH^bC(O)Ar), 3.61 (3H, s, CO₂CH₃), 3.98 (1H, q, J 7.8, pyrrolizine(2)H), 4.12 (1H, dd, J 7.8, 10.9, pyrrolizine(3)H^aH^b), 4.19-4.27 (2H, m, pyrrolizine(3)H^aH^b and pyrrolizine(1)H), 5.75 (1H, d, J 3.5, pyrrolizine(7)H), 5.97 (1H,

d, *J* 3.5, pyrrolizine(6)*H*), 7.44-7.47 (2H, m, C(O)Ar(3,5)*H*), 7.55-7.58 (1H, m, C(O)Ar(4)*H*), 7.90-7.92 (2H, m, C(O)Ar(2,6)*H*); ¹³C NMR (125 MHz, CDCl₃) 36.5 (pyrrolizineC(1)H), 39.9 (pyrrolizineC(2)H), 46.5 (pyrrolizine(1)CH^aH^bC(O)Ar), 49.3 (pyrrolizineC(3)H), 52.2 (CO₂CH₃), 100.9 (pyrrolizineC(7)H), 109.5 (pyrrolizineC(6)H), 110.1 (), 128.1 (C(O)ArC(3,5)H), 128.8 (C(O)ArC(2,6)H), 133.4 (pyrrolizineC(8)). 136.6 (C(O)ArC(1)), 136.8 (pyrrolizineC(5)Cl), 171.9 (CO₂Me), 197.7 (C(O)Ar); HRMS (NSI⁺), C₁₇H₁₇ClNO₃ [M+H]⁺, requires 318.0891, found 318.0893 (+0.6 ppm).

1.4 Computational Details

Calculations were run with Gaussian 09 Revision D.01.^[8] Geometry optimisations were performed using the M06-2X functional^[9] using 6-31G** basis sets^[10] on all atoms (called BS1). All stationary points were fully characterized via analytical frequency calculations as either minima (all positive eigenvalues) or transition states (one negative eigenvalue) and IRC calculations and subsequent geometry optimizations were used to confirm the minima linked by each transition state. Frequency calculations also provided a free energy in the gas-phase, computed at 298.15 K and 1 atm. SCF energies were recomputed with the larger 6-311++G** basis set^[11] (BS2) and incorporate a correction for CH₂Cl₂ solvent (CH₂Cl₂, PCM approach^[12]). An equivalent set of results were also generated with the B3LYP functional.^[13] Reaction profiles computed with the M06-2X functional, including the reaction of (*E*)-**45** to give **21_{trans}** are given in Figure S1 while those computed with the B3LYP functional are given in Figure S2. With this latter functional the reactions of (*Z*)-**45** yielded no intermediate corresponding to **47** and the lactonisation step leads directly to products.

1.5 Computed Reaction Profiles and Labelling Schemes

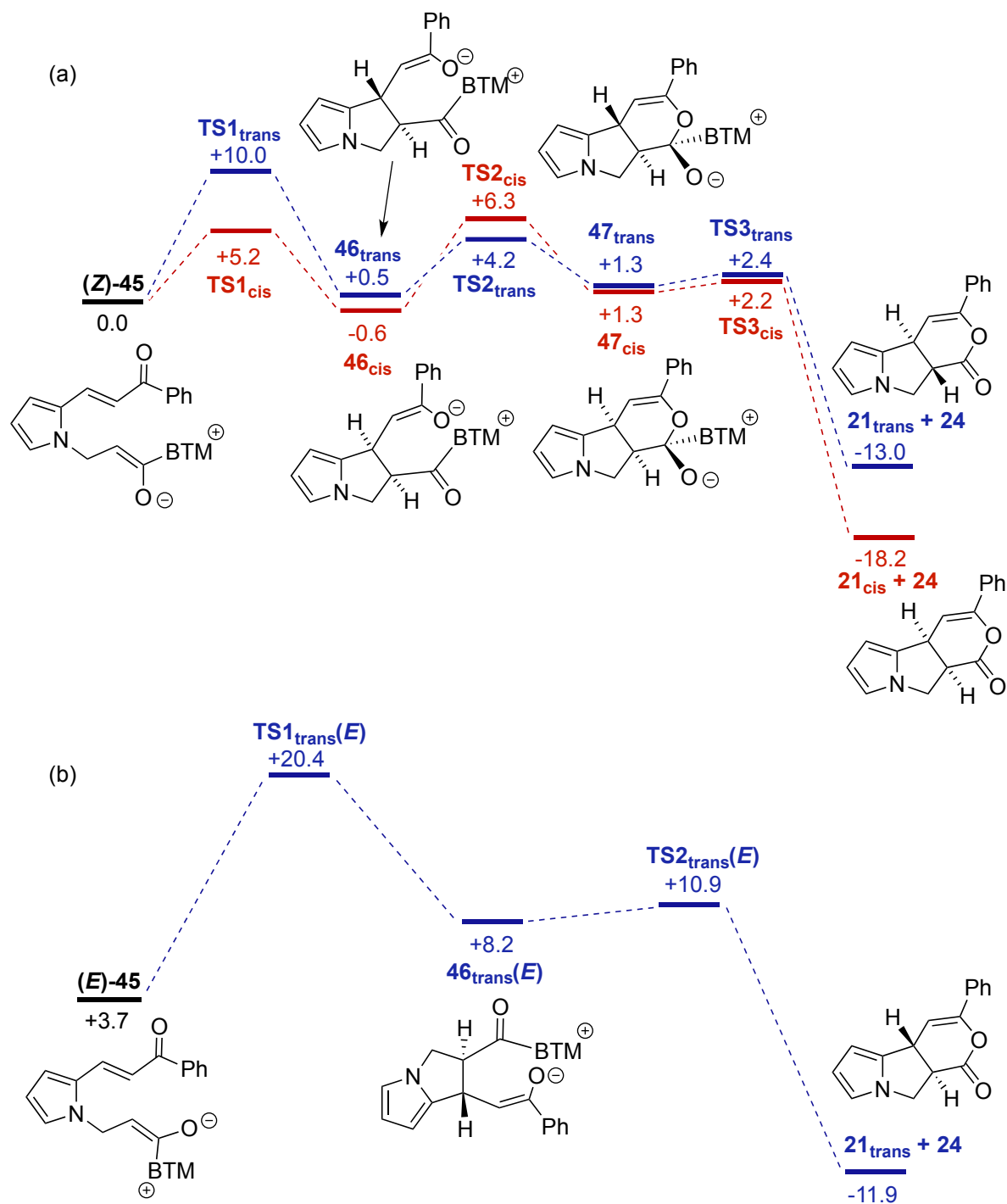


Figure S1. Reaction profiles (free energies, kcal/mol) computed with the M06-2X functional for the formation of cis- and trans-isomers of **21** from (a) **(Z)-45** (as shown in the main text) and (b) **(E)-45**. Free energies include corrections from dichloromethane solvent.

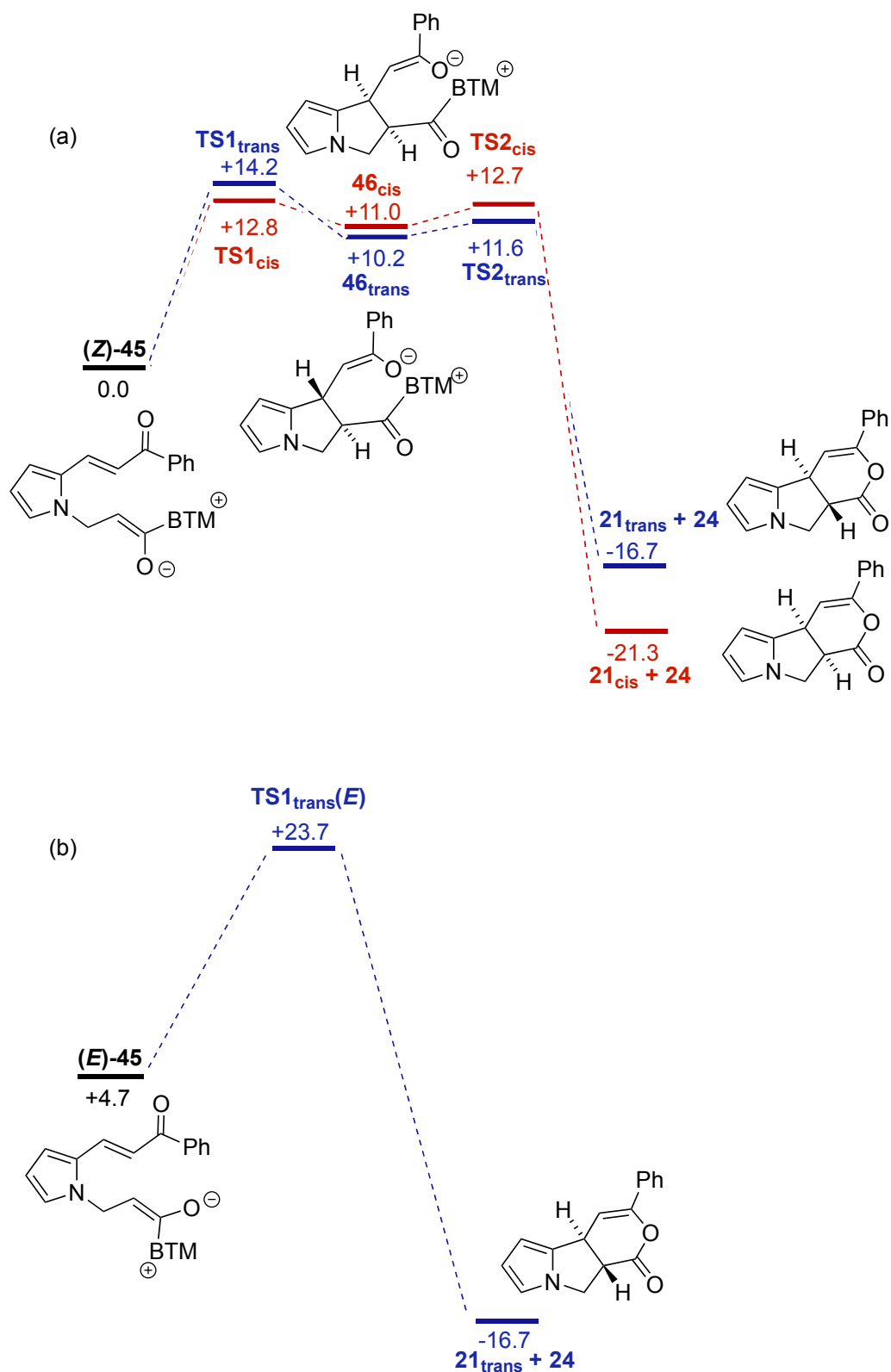


Figure S2. Reaction profiles (free energies, kcal/mol) computed with the B3LYP functional for the formation of cis- and trans-isomers of **21** from (a) **(Z)-45** and (b) **(E)-45**. Free energies include corrections from dichloromethane solvent.

1.6 Computed Cartesian Coordinates (Å) and Energies (au) for all stationary points.

1.6.1 M06-2X

(a) Formation of 21_{cis} from (Z)-45

```

62
(Z)-45
H   3.33461  4.23186 -0.35319
C   5.17620  3.09701 -0.90928
C   3.80625  3.31606 -0.68156
H   5.98590  3.79508 -0.75865
H  -1.85300  5.65736  2.71902
H  -4.11972  4.69893  3.00990
C  -3.39179  4.19127  2.38488
C  -2.11733  4.72860  2.22394
H  -0.19757  4.52049  1.29608
C  -1.17986  4.07947  1.42534
C  -1.51091  2.88504  0.78016
C  -2.79952  2.36052  0.93539
C  -3.73299  3.00572  1.73554
H  -4.72904  2.58917  1.84929
H  -3.04812  1.44648  0.40363
H   6.17476  1.22621 -1.63641
O  -0.98089  1.14463 -0.71252
H   1.24019  3.21147  0.59892
C   0.85936  2.49645 -0.12196
C  -0.55365  2.11758 -0.09101
C   1.70907  1.87861 -0.97844
H   1.28803  1.16140 -1.68033
C   3.12612  2.14996 -1.02540
C   5.29661  1.79778 -1.37181
N   4.06562  1.23353 -1.45217
C   3.81794 -0.18037 -1.83093
C   2.83052 -0.84818 -0.94019
H   3.03738 -0.94657  0.11717
H   3.43607 -0.21098 -2.85614
O   1.21225 -1.18286 -2.66550
C   1.62147 -1.18400 -1.48255
S  -1.38281 -1.65418 -2.51599
C  -2.99908 -1.55641 -1.76948
C  -2.92213 -1.42143 -0.37679
C  -4.05874 -1.26228  0.40735
N  -1.60471 -1.48236  0.05019
C  -0.70036 -1.56036 -0.93643
N   0.54385 -1.49395 -0.51209
C   0.55506 -1.15017  0.92585
H  -1.19261 -1.85661  2.08699
C  -0.96342 -1.12370  1.30941
H  -1.29730 -0.12761  1.61715
H   4.80942 -0.64760 -1.82207
H   0.98918 -0.14778  1.01060
C   1.34333 -2.13371  1.75870
C   2.11534 -1.67565  2.82445

```

```

C   2.79643 -2.57909  3.63646
C   2.71053 -3.94447  3.38246
C   1.94459 -4.40524  2.31314
C   1.26223 -3.50344  1.50434
H   2.19239 -0.60740  3.01085
H   3.40086 -2.21526  4.46098
H   3.24629 -4.64886  4.01040
H   1.88517 -5.46862  2.10513
H   0.67915 -3.85646  0.65746
H  -3.97928 -1.15347  1.48429
C  -5.29148 -1.24118 -0.23871
H  -6.19609 -1.11447  0.34614
C  -5.37993 -1.38501 -1.62508
H  -6.35176 -1.36838 -2.10583
C  -4.23470 -1.54213 -2.40305
H  -4.30520 -1.63980 -3.48145

```

```

SCF      =      -1520.57793395
H(0 K)=      -1520.081400
H(298 K)=      -1520.051438
G(298 K)=      -1520.144988
SCF (BS2) =      -1520.94865112
SCF(DCM) =      -1520.59758708
Lowest Frequency = 15.8198cm-1

```

```

62
TS1cis
H  -5.68136 -2.50848 -0.42980
C  -4.62616 -2.31515 -0.59872
C  -4.22568 -1.43810 -1.60380
H  -4.96892 -0.94267 -2.22154
C  -2.31130 -2.69702 -0.02296
H  -2.53428 -0.50973 -2.58549
C  -2.87275 -1.19070 -1.81080
H  -1.58040 -3.18540  0.61216
C  -1.89727 -1.81132 -1.02456
C  -3.66437 -2.94584  0.18846
H  -3.96870 -3.63564  0.97008
C  -0.45261 -1.43661 -1.27872
O  -0.24318 -0.50988 -2.09986
H   0.34025 -2.88799  0.14873
C  -0.61259  0.79819  0.78368
C  -2.72024  1.43880  0.14876
C  -3.00428  0.62392  1.25262
S  -1.52311 -0.02816  1.98961
C   0.57037 -2.11159 -0.56840
C   1.60225 -0.02445  1.18638
O   1.15508 -0.57943  2.18523
C   1.92159 -1.78077 -0.77443
C   2.77934 -0.32300  0.46031
H   2.10553 -1.19921 -1.67821
N   0.68950  0.88399  0.53361
C  -3.72647  2.05585 -0.58417
N  -1.35125  1.50135 -0.07204
C  -0.52311  2.15691 -1.08412
H  -0.62531  3.24303 -1.00261
H  -0.80438  1.79355 -2.07304
C   0.91363  1.67237 -0.70688
C   3.83628 -1.12933  1.16475
H   3.54517 -1.30482  2.20564
H   4.80785 -0.62506  1.14916

```


| | | | |
|---|----------|----------|----------|
| C | 4.80285 | -3.44971 | 0.67088 |
| H | 5.63659 | -3.36213 | 1.35168 |
| C | 4.36401 | -4.50511 | -0.09962 |
| N | 3.94636 | -2.40525 | 0.46665 |
| C | 2.95966 | -2.77129 | -0.40092 |
| C | 3.18767 | -4.08003 | -0.77418 |
| H | 2.58664 | -4.64398 | -1.47205 |
| H | 4.83847 | -5.47317 | -0.17295 |
| H | 3.12304 | 0.41129 | -0.25971 |
| C | 1.90110 | 2.79558 | -0.50872 |
| H | 1.24363 | 0.97602 | -1.48099 |
| C | 1.84159 | 3.62668 | 0.61202 |
| C | 2.74222 | 4.67696 | 0.75120 |
| C | 3.70606 | 4.90709 | -0.22958 |
| C | 3.76885 | 4.08149 | -1.34762 |
| C | 2.86933 | 3.02731 | -1.48456 |
| H | 1.09827 | 3.44062 | 1.38389 |
| H | 2.69707 | 5.31420 | 1.62833 |
| H | 4.41056 | 5.72454 | -0.11700 |
| H | 4.52176 | 4.25098 | -2.11023 |
| H | 2.92083 | 2.37377 | -2.35167 |
| H | -3.48803 | 2.67727 | -1.44057 |
| C | -5.03966 | 1.82958 | -0.18705 |
| H | -5.84846 | 2.29495 | -0.73980 |
| C | -5.33365 | 1.00834 | 0.90505 |
| H | -6.36718 | 0.83977 | 1.18650 |
| C | -4.31955 | 0.39383 | 1.63435 |
| H | -4.54920 | -0.25445 | 2.47320 |

SCF = -1520.57045438
H(0 K) = -1520.074169
H(298 K) = -1520.045209
G(298 K) = -1520.135459
SCF (BS2) = -1520.94239287
SCF(DCM) = -1520.59017197
Lowest Frequency = -325.4725cm⁻¹

62

46cis

| | | | |
|---|----------|----------|----------|
| H | -5.63593 | -2.74271 | -0.19301 |
| C | -4.58950 | -2.50721 | -0.36456 |
| C | -4.21707 | -1.67603 | -1.41803 |
| H | -4.97514 | -1.25856 | -2.07522 |
| C | -2.26315 | -2.73250 | 0.25443 |
| H | -2.55643 | -0.71803 | -2.43203 |
| C | -2.87453 | -1.37381 | -1.62792 |
| H | -1.51263 | -3.12920 | 0.93093 |
| C | -1.87554 | -1.89876 | -0.80155 |
| C | -3.60479 | -3.03346 | 0.47163 |
| H | -3.88349 | -3.68261 | 1.29709 |
| C | -0.44985 | -1.45208 | -1.05343 |
| O | -0.31332 | -0.46185 | -1.85928 |
| H | 0.43307 | -2.94430 | 0.23553 |
| C | -0.68204 | 0.95616 | 0.79222 |
| C | -2.72099 | 1.53880 | -0.04487 |
| C | -3.09275 | 0.76120 | 1.05985 |
| S | -1.67748 | 0.18292 | 1.95663 |
| C | 0.58338 | -2.06907 | -0.38386 |
| C | 1.43158 | -0.02193 | 1.26000 |
| O | 1.04893 | -0.40063 | 2.34268 |
| C | 1.98992 | -1.60441 | -0.61399 |

| | | | |
|---|----------|----------|----------|
| C | 2.58427 | -0.57270 | 0.48355 |
| H | 2.00752 | -1.09467 | -1.58460 |
| N | 0.64269 | 0.94929 | 0.58825 |
| C | -3.66700 | 2.08270 | -0.90554 |
| N | -1.33883 | 1.63912 | -0.13097 |
| C | -0.43857 | 2.17597 | -1.15425 |
| H | -0.49462 | 3.26830 | -1.15924 |
| H | -0.70024 | 1.73162 | -2.11440 |
| C | 0.95852 | 1.65997 | -0.68503 |
| C | 3.55289 | -1.37942 | 1.36606 |
| H | 3.05834 | -1.70951 | 2.28507 |
| H | 4.44611 | -0.80668 | 1.63015 |
| C | 4.78141 | -3.52892 | 0.58606 |
| H | 5.53529 | -3.56905 | 1.35753 |
| C | 4.50382 | -4.37912 | -0.46354 |
| N | 3.88073 | -2.50244 | 0.51309 |
| C | 3.03165 | -2.68442 | -0.53983 |
| C | 3.39020 | -3.84978 | -1.17795 |
| H | 2.91357 | -4.26959 | -2.05080 |
| H | 5.05009 | -5.28104 | -0.70001 |
| H | 3.11666 | 0.23342 | -0.03077 |
| C | 1.98348 | 2.74688 | -0.47750 |
| H | 1.28005 | 0.90980 | -1.40895 |
| C | 1.85465 | 3.67584 | 0.55810 |
| C | 2.79558 | 4.68748 | 0.71194 |
| C | 3.87159 | 4.78021 | -0.17015 |
| C | 4.00526 | 3.85723 | -1.20228 |
| C | 3.06398 | 2.84114 | -1.35312 |
| H | 1.02013 | 3.59910 | 1.25193 |
| H | 2.69261 | 5.40338 | 1.52078 |
| H | 4.60686 | 5.56859 | -0.04751 |
| H | 4.84430 | 3.92167 | -1.88707 |
| H | 3.16804 | 2.11230 | -2.15296 |
| H | -3.36417 | 2.67022 | -1.76521 |
| C | -5.00414 | 1.82273 | -0.63150 |
| H | -5.76682 | 2.22499 | -1.28913 |
| C | -5.38202 | 1.04441 | 0.46775 |
| H | -6.43277 | 0.84733 | 0.64861 |
| C | -4.43126 | 0.50142 | 1.32496 |
| H | -4.72177 | -0.12441 | 2.16136 |

SCF = -1520.58086231
H(0 K) = -1520.082168
H(298 K) = -1520.053440
G(298 K) = -1520.141603
SCF (BS2) = -1520.95375291
SCF(DCM) = -1520.60266181
Lowest Frequency = 25.0511cm⁻¹

62

TS2cis

| | | | |
|---|---------|---------|----------|
| H | 4.31902 | 5.25267 | -0.39454 |
| C | 3.43422 | 4.62797 | -0.46979 |
| C | 3.55491 | 3.25952 | -0.69522 |
| H | 4.53875 | 2.80988 | -0.80171 |
| C | 1.02913 | 4.39461 | -0.44424 |
| H | 2.48856 | 1.39632 | -0.96949 |
| C | 2.41677 | 2.46457 | -0.79098 |
| H | 0.04892 | 4.84852 | -0.33954 |
| C | 1.13808 | 3.01677 | -0.66318 |
| C | 2.16427 | 5.19099 | -0.34759 |

| | | | |
|--------------------|----------|---------------------------|----------|
| H | 2.05887 | 6.25763 | -0.17299 |
| C | -0.04033 | 2.10110 | -0.74884 |
| O | 0.21400 | 0.82293 | -0.84937 |
| H | -1.64887 | 3.53084 | -0.48411 |
| C | 1.20586 | -1.13487 | 0.65524 |
| C | 3.22575 | -1.85383 | -0.15609 |
| C | 3.63213 | -0.97074 | 0.85289 |
| S | 2.24620 | -0.21658 | 1.66835 |
| C | -1.33327 | 2.50870 | -0.64333 |
| C | -0.77738 | 0.09173 | 0.91845 |
| O | -0.28038 | 0.68191 | 1.85803 |
| C | -2.35948 | 1.41718 | -0.70125 |
| C | -2.18623 | 0.31967 | 0.43771 |
| H | -2.28168 | 0.88741 | -1.66077 |
| N | -0.12149 | -1.16705 | 0.53767 |
| C | 4.14446 | -2.53455 | -0.94753 |
| N | 1.83954 | -1.91328 | -0.21947 |
| C | 0.90125 | -2.51516 | -1.16181 |
| H | 0.89397 | -3.60297 | -1.05099 |
| H | 1.17358 | -2.24425 | -2.18416 |
| C | -0.45793 | -1.88031 | -0.72458 |
| C | -3.08232 | 0.82826 | 1.58506 |
| H | -2.52194 | 1.51820 | 2.22318 |
| H | -3.48858 | 0.01696 | 2.19532 |
| C | -5.36714 | 2.00629 | 1.14777 |
| H | -5.83396 | 1.82838 | 2.10460 |
| C | -5.80884 | 2.68437 | 0.03087 |
| N | -4.12705 | 1.51540 | 0.85049 |
| C | -3.76061 | 1.87642 | -0.41445 |
| C | -4.78902 | 2.60816 | -0.96281 |
| H | -4.81478 | 3.03517 | -1.95431 |
| H | -6.76869 | 3.17091 | -0.06828 |
| H | -2.60607 | -0.61813 | 0.06083 |
| C | -1.54317 | -2.91233 | -0.54070 |
| H | -0.74368 | -1.10286 | -1.43903 |
| C | -1.49603 | -3.80108 | 0.53559 |
| C | -2.47260 | -4.77964 | 0.67884 |
| C | -3.50366 | -4.87819 | -0.25435 |
| C | -3.55775 | -3.99182 | -1.32533 |
| C | -2.58009 | -3.00898 | -1.46718 |
| H | -0.70004 | -3.71123 | 1.27106 |
| H | -2.43433 | -5.46231 | 1.52137 |
| H | -4.26781 | -5.63992 | -0.14023 |
| H | -4.36466 | -4.05759 | -2.04756 |
| H | -2.62832 | -2.30517 | -2.29440 |
| H | 3.81377 | -3.21408 | -1.72571 |
| C | 5.49380 | -2.30662 | -0.70450 |
| H | 6.23535 | -2.82030 | -1.30613 |
| C | 5.90939 | -1.42580 | 0.29937 |
| H | 6.96853 | -1.26556 | 0.46683 |
| C | 4.98442 | -0.74739 | 1.08660 |
| H | 5.30742 | -0.05764 | 1.85907 |
| | | | |
| SCF | = | -1520.56751370 | |
| H(0 K)= | | -1520.069736 | |
| H(298 K)= | | -1520.041394 | |
| G(298 K)= | | -1520.130949 | |
| SCF (BS2) = | | -1520.93799971 | |
| SCF(DCM) = | | -1520.59134609 | |
| Lowest Frequency = | | -133.2045cm ⁻¹ | |

| | | | |
|-------|----------|----------|----------|
| 62 | | | |
| 47cis | | | |
| H | -0.52480 | 7.09221 | -1.24750 |
| C | -0.73179 | 6.03194 | -1.14070 |
| C | 0.14634 | 5.21490 | -0.43127 |
| H | 1.03549 | 5.64107 | 0.02330 |
| C | -2.13907 | 4.12382 | -1.58629 |
| H | 0.54521 | 3.20100 | 0.26512 |
| C | -0.11344 | 3.85551 | -0.29842 |
| H | -3.01718 | 3.68819 | -2.05402 |
| C | -1.26439 | 3.30285 | -0.86955 |
| C | -1.87482 | 5.48284 | -1.71770 |
| H | -2.55617 | 6.11317 | -2.28073 |
| C | -1.53351 | 1.86379 | -0.67660 |
| O | -0.40932 | 1.09166 | -0.56649 |
| H | -3.64805 | 1.87247 | -0.59194 |
| C | 1.99782 | -0.39229 | 0.39753 |
| C | 4.24556 | -0.60538 | -0.08814 |
| C | 4.28181 | 0.23777 | 1.03170 |
| S | 2.64471 | 0.63276 | 1.63431 |
| C | -2.73592 | 1.28777 | -0.56740 |
| C | -0.37986 | 0.24396 | 0.65643 |
| O | 0.04976 | 0.82236 | 1.68923 |
| C | -2.79490 | -0.19300 | -0.27810 |
| C | -1.69466 | -0.56544 | 0.76362 |
| H | -2.65971 | -0.77516 | -1.19952 |
| N | 0.77373 | -0.75006 | 0.10757 |
| C | 5.40653 | -1.02760 | -0.72392 |
| N | 2.93199 | -0.90650 | -0.42419 |
| C | 2.30492 | -1.75796 | -1.42835 |
| H | 2.52895 | -2.81130 | -1.22900 |
| H | 2.64424 | -1.49790 | -2.43330 |
| C | 0.79027 | -1.44223 | -1.20349 |
| C | -2.37981 | -0.34785 | 2.12680 |
| H | -2.26701 | 0.68907 | 2.45462 |
| H | -1.98879 | -1.00781 | 2.90376 |
| C | -4.90224 | -0.92583 | 2.50521 |
| H | -4.89370 | -1.03082 | 3.57945 |
| C | -5.92978 | -1.03177 | 1.58967 |
| N | -3.76355 | -0.66132 | 1.80191 |
| C | -4.03960 | -0.58274 | 0.46724 |
| C | -5.38610 | -0.80902 | 0.29090 |
| H | -5.92083 | -0.82240 | -0.64739 |
| H | -6.95936 | -1.25984 | 1.82590 |
| H | -1.47878 | -1.63235 | 0.66229 |
| C | -0.06989 | -2.68248 | -1.23070 |
| H | 0.43130 | -0.71906 | -1.94440 |
| C | 0.08536 | -3.66270 | -0.24618 |
| C | -0.70455 | -4.80512 | -0.26387 |
| C | -1.65442 | -4.98115 | -1.27020 |
| C | -1.80880 | -4.01217 | -2.25536 |
| C | -1.01743 | -2.86424 | -2.23490 |
| H | 0.80859 | -3.51028 | 0.55192 |
| H | -0.58711 | -5.55598 | 0.51050 |
| H | -2.27660 | -5.86983 | -1.27947 |
| H | -2.55153 | -4.14172 | -3.03540 |
| H | -1.14587 | -2.09915 | -2.99624 |
| H | 5.36258 | -1.68033 | -1.58934 |
| C | 6.62210 | -0.58271 | -0.21122 |
| H | 7.54476 | -0.89747 | -0.68644 |
| C | 6.67009 | 0.25994 | 0.90107 |

H 7.62896 0.59355 1.28181
 C 5.49985 0.67912 1.53102
 H 5.53736 1.33421 2.39531

SCF = -1520.58316728
 H(0 K)= -1520.084567
 H(298 K)= -1520.055876
 G(298 K)= -1520.146536
 SCF (BS2) = -1520.94938367
 SCF(DCM) = -1520.60363005
 Lowest Frequency = 14.3213cm⁻¹

62

TS3cis

H -0.73537 7.09518 -1.34020
 C -0.90534 6.03176 -1.20385
 C -0.02028 5.27367 -0.44030
 H 0.83704 5.74820 0.02703
 C -2.22336 4.05638 -1.62928
 H 0.43670 3.30204 0.33164
 C -0.23246 3.91018 -0.26950
 H -3.06706 3.57240 -2.11225
 C -1.34249 3.29408 -0.85665
 C -2.00705 5.41948 -1.79790
 H -2.69287 6.00406 -2.40313
 C -1.56329 1.85224 -0.62638
 O -0.40791 1.14209 -0.41912
 H -3.67476 1.76402 -0.68671
 C 2.02590 -0.39204 0.42236
 C 4.27407 -0.52456 -0.12404
 C 4.32076 0.26259 1.03633
 S 2.69460 0.59029 1.69496
 C -2.74236 1.22227 -0.57924
 C -0.42539 0.29893 0.78002
 O 0.02285 0.81457 1.81528
 C -2.76358 -0.25268 -0.25476
 C -1.70158 -0.55943 0.84429
 H -2.56789 -0.85215 -1.15380
 N 0.81048 -0.76713 0.15473
 C 5.43141 -0.88838 -0.80155
 N 2.96223 -0.83448 -0.44937
 C 2.33490 -1.68107 -1.45627
 H 2.59350 -2.73244 -1.28705
 H 2.63720 -1.39013 -2.46455
 C 0.81927 -1.41198 -1.17636
 C -2.45407 -0.33803 2.17168
 H -2.39493 0.70847 2.48479
 H -2.07487 -0.96793 2.97857
 C -4.96990 -0.99027 2.45091
 H -5.00656 -1.07018 3.52669
 C -5.95083 -1.15143 1.49349
 N -3.80950 -0.70483 1.79231
 C -4.02761 -0.66620 0.44489
 C -5.35653 -0.94127 0.21485
 H -5.84720 -0.99606 -0.74576
 H -6.98222 -1.40731 1.68956
 H -1.43050 -1.61605 0.77916
 C -0.01232 -2.67120 -1.22532
 H 0.42450 -0.67588 -1.88725
 C 0.13747 -3.64626 -0.23494
 C -0.61636 -4.81257 -0.27919

C -1.52510 -5.01770 -1.31695
 C -1.67550 -4.05293 -2.30716
 C -0.92044 -2.88182 -2.26032
 H 0.82969 -3.47148 0.58552
 H -0.50238 -5.55979 0.49930
 H -2.11954 -5.92479 -1.34671
 H -2.38766 -4.20419 -3.11153
 H -1.04595 -2.12118 -3.02684
 H 5.38286 -1.49771 -1.69778
 C 6.64903 -0.44438 -0.29154
 H 7.56700 -0.71577 -0.80129
 C 6.70457 0.34194 0.86015
 H 7.66411 0.67626 1.23846
 C 5.53872 0.70449 1.53315
 H 5.58006 1.31662 2.42816

SCF = -1520.58280508
 H(0 K)= -1520.085090
 H(298 K)= -1520.056779
 G(298 K)= -1520.147213
 SCF (BS2) = -1520.94886926
 SCF(DCM) = -1520.60151674
 Lowest Frequency = -143.6195cm⁻¹

30

24

C -0.37710 -0.92916 -1.22428
 C 0.42125 1.11372 -0.57912
 H -0.78329 -1.77933 -0.67111
 H 0.00492 -1.27039 -2.19472
 N -0.68409 1.48845 -1.08559
 N 0.66646 -0.24585 -0.48043
 S 1.79485 2.03818 0.04329
 C -2.58860 0.04644 -0.41591
 C -3.67420 -0.73814 -0.81046
 C -2.57127 0.58426 0.87025
 C -4.72459 -0.98792 0.06700
 H -3.69850 -1.15162 -1.81640
 C -3.62164 0.33476 1.74969
 H -1.74040 1.21418 1.17148
 C -4.69899 -0.45219 1.35228
 H -5.56576 -1.59431 -0.25395
 H -3.59950 0.76077 2.74787
 H -5.51815 -0.64229 2.03836
 C -1.42130 0.23987 -1.36656
 H -1.80673 0.27321 -2.38999
 C 2.49263 -1.87590 -0.04280
 C 3.81148 -2.01141 0.39000
 C 4.56750 -0.89996 0.75485
 C 4.01971 0.38310 0.68683
 C 2.71328 0.52460 0.25135
 C 1.94623 -0.59939 -0.10644
 H 1.89875 -2.74007 -0.32123
 H 4.25110 -3.00166 0.44469
 H 5.59005 -1.02637 1.09230
 H 4.60705 1.25288 0.96213

SCF = -698.207579658
 H(0 K)= -697.969189
 H(298 K)= -697.955637
 G(298 K)= -698.011487

SCF (BS2) = -698.364477812
 SCF(DCM) = -698.21608794
 Lowest Frequency = 27.1554cm⁻¹

32

21cis

| | | | |
|---|----------|----------|----------|
| H | 5.82010 | -1.62107 | -0.56137 |
| C | 4.82388 | -1.23321 | -0.37496 |
| C | 4.61851 | 0.13713 | -0.24517 |
| H | 5.45506 | 0.82333 | -0.32807 |
| C | 2.46499 | -1.61106 | -0.04260 |
| H | 3.17920 | 1.70397 | 0.09099 |
| C | 3.34213 | 0.63684 | -0.00818 |
| H | 1.62197 | -2.29338 | -0.00276 |
| C | 2.25522 | -0.23566 | 0.10771 |
| C | 3.74187 | -2.10545 | -0.27565 |
| H | 3.89086 | -3.17380 | -0.39429 |
| C | 0.90501 | 0.29316 | 0.38949 |
| O | 0.80268 | 1.63013 | 0.02786 |
| H | 0.07190 | -1.39883 | 1.28310 |
| C | -0.09546 | -0.37673 | 0.96562 |
| C | -0.38094 | 2.29821 | 0.08410 |
| O | -0.38719 | 3.48366 | -0.08943 |
| C | -1.46291 | 0.21640 | 1.17205 |
| C | -1.62853 | 1.47109 | 0.27970 |
| H | -1.62779 | 0.45280 | 2.22913 |
| C | -2.14386 | 0.91731 | -1.07622 |
| H | -1.31576 | 0.63176 | -1.73703 |
| H | -2.78126 | 1.63583 | -1.59501 |
| C | -3.78812 | -1.10370 | -1.19668 |
| H | -4.19470 | -0.93481 | -2.18200 |
| C | -4.03543 | -2.09371 | -0.26922 |
| N | -2.88106 | -0.24985 | -0.63603 |
| C | -2.53740 | -0.67977 | 0.61484 |
| C | -3.23862 | -1.83111 | 0.88374 |
| H | -3.20167 | -2.41288 | 1.79268 |
| H | -4.73056 | -2.91061 | -0.39670 |
| H | -2.38602 | 2.13782 | 0.69454 |

SCF = -822.386011564
 H(0 K) = -822.127591
 H(298 K) = -822.113487
 G(298 K) = -822.170084
 SCF (BS2) = -822.597470569
 SCF(DCM) = -822.395396679
 Lowest Frequency = 36.2883cm⁻¹

(b) Formation of 21_{trans} from (Z)-45

62

TS1_{trans}

| | | | |
|---|----------|----------|----------|
| C | 1.40854 | 1.89966 | -0.13653 |
| C | -0.00731 | 1.98635 | -0.12701 |
| C | 1.31016 | -1.48706 | -1.20996 |
| H | 2.00960 | 2.43886 | 0.58554 |
| C | 5.58142 | 0.72554 | -1.85918 |
| H | 6.37809 | 0.02108 | -2.04762 |
| C | 4.26095 | 2.51512 | -1.47011 |
| H | 3.89065 | 3.52364 | -1.35851 |
| C | 5.58146 | 2.10373 | -1.79657 |
| H | 6.43848 | 2.74185 | -1.95628 |

| | | | |
|---|----------|----------|----------|
| N | 4.31262 | 0.30046 | -1.59193 |
| C | 3.49981 | 1.36907 | -1.35682 |
| C | 3.74725 | -1.03986 | -1.47274 |
| H | 3.51584 | -1.44957 | -2.46134 |
| H | 4.48527 | -1.68839 | -0.98793 |
| O | 1.08889 | -1.84143 | -2.36580 |
| O | -0.75010 | 1.24957 | -0.81571 |
| C | -0.68585 | 2.97435 | 0.79773 |
| C | -2.08243 | 2.92921 | 0.87654 |
| C | -0.00208 | 3.91622 | 1.57283 |
| C | -2.77831 | 3.78387 | 1.72413 |
| H | -2.59932 | 2.21442 | 0.24224 |
| C | -0.69681 | 4.77327 | 2.42107 |
| H | 1.07713 | 3.99825 | 1.50514 |
| C | -2.08563 | 4.70678 | 2.50447 |
| H | -3.86230 | 3.73701 | 1.77179 |
| H | -0.15171 | 5.50067 | 3.01458 |
| H | -2.62497 | 5.37708 | 3.16656 |
| C | -1.40980 | -0.73135 | 1.30274 |
| C | -1.05999 | -1.43599 | -0.86511 |
| H | -1.81595 | -1.36605 | 2.09487 |
| H | -1.60530 | 0.32340 | 1.51252 |
| N | 0.15305 | -1.49945 | -0.33469 |
| N | -1.99663 | -1.08774 | 0.01370 |
| S | -1.63553 | -1.63521 | -2.47469 |
| C | 2.06771 | 1.11218 | -1.09734 |
| C | 2.48122 | -0.90216 | -0.67018 |
| H | 2.59283 | -0.88333 | 0.40862 |
| H | 1.45966 | 0.84085 | -1.96275 |
| C | 0.69933 | -1.99777 | 2.04078 |
| C | 1.55969 | -1.54623 | 3.03971 |
| C | 0.36453 | -3.35177 | 1.97904 |
| C | 2.07892 | -2.43806 | 3.97557 |
| H | 1.82885 | -0.49334 | 3.07728 |
| C | 0.88577 | -4.24289 | 2.91047 |
| H | -0.29439 | -3.70830 | 1.19063 |
| C | 1.74218 | -3.78639 | 3.91138 |
| H | 2.75172 | -2.07925 | 4.74744 |
| H | 0.62796 | -5.29548 | 2.85423 |
| H | 2.15000 | -4.48396 | 4.63555 |
| C | 0.11014 | -1.00666 | 1.06590 |
| H | 0.66341 | -0.06473 | 1.10096 |
| C | -4.39269 | -0.41674 | 0.11708 |
| C | -5.54850 | -0.26685 | -0.64078 |
| C | -5.55971 | -0.55995 | -2.00770 |
| C | -4.40970 | -1.00210 | -2.65544 |
| C | -3.24818 | -1.14674 | -1.90731 |
| C | -3.24886 | -0.86098 | -0.53631 |
| H | -4.37291 | -0.18776 | 1.17742 |
| H | -6.45552 | 0.08485 | -0.16160 |
| H | -6.47520 | -0.43511 | -2.57505 |
| H | -4.41612 | -1.21613 | -3.71887 |

SCF = -1520.56334604
 H(0 K) = -1520.067232
 H(298 K) = -1520.038106
 G(298 K) = -1520.129413
 SCF (BS2) = -1520.93417690
 SCF(DCM) = -1520.58264494
 Lowest Frequency = -353.9720cm⁻¹

62
46trans

| | | | |
|---|----------|----------|----------|
| C | 1.56637 | 1.86015 | -0.12101 |
| C | 0.19120 | 1.91209 | -0.15865 |
| C | 1.13549 | -1.24710 | -1.30712 |
| H | 2.15963 | 2.51504 | 0.50552 |
| C | 5.76995 | 0.45226 | -1.74054 |
| H | 6.49855 | -0.32133 | -1.92991 |
| C | 4.61369 | 2.36757 | -1.35031 |
| H | 4.36093 | 3.40752 | -1.20710 |
| C | 5.90099 | 1.82052 | -1.63199 |
| H | 6.82672 | 2.36959 | -1.72842 |
| N | 4.45129 | 0.16252 | -1.52313 |
| C | 3.74114 | 1.30613 | -1.29728 |
| C | 3.63723 | -1.03619 | -1.55685 |
| H | 3.39695 | -1.32877 | -2.58455 |
| H | 4.13349 | -1.86982 | -1.05255 |
| O | 0.95896 | -1.62248 | -2.44424 |
| O | -0.53412 | 1.18290 | -0.92548 |
| C | -0.55768 | 2.80389 | 0.80746 |
| C | -1.91229 | 3.04725 | 0.54908 |
| C | 0.00273 | 3.33920 | 1.97295 |
| C | -2.67847 | 3.82159 | 1.41501 |
| H | -2.33436 | 2.60547 | -0.34844 |
| C | -0.76208 | 4.11292 | 2.84103 |
| H | 1.04136 | 3.13208 | 2.21203 |
| C | -2.10568 | 4.36001 | 2.56529 |
| H | -3.72500 | 4.00991 | 1.19137 |
| H | -0.31062 | 4.51834 | 3.74178 |
| H | -2.70112 | 4.96321 | 3.24379 |
| C | -1.44963 | -0.57535 | 1.27605 |
| C | -1.18297 | -1.34369 | -0.87946 |
| H | -1.85843 | -1.15047 | 2.11072 |
| H | -1.60552 | 0.49772 | 1.41552 |
| N | 0.06252 | -1.41204 | -0.38635 |
| N | -2.08142 | -0.98139 | 0.02159 |
| S | -1.80656 | -1.55174 | -2.46457 |
| C | 2.28055 | 1.00777 | -1.11977 |
| C | 2.37241 | -0.56401 | -0.81508 |
| H | 2.50717 | -0.69610 | 0.26117 |
| H | 1.75950 | 1.08337 | -2.08759 |
| C | 0.62996 | -1.91989 | 1.97700 |
| C | 1.62758 | -1.52218 | 2.86520 |
| C | 0.16823 | -3.23793 | 2.00286 |
| C | 2.15808 | -2.43202 | 3.77799 |
| H | 1.98828 | -0.49639 | 2.83475 |
| C | 0.69783 | -4.14625 | 2.91188 |
| H | -0.60133 | -3.55418 | 1.30143 |
| C | 1.69320 | -3.74275 | 3.80178 |
| H | 2.93588 | -2.11557 | 4.46506 |
| H | 0.33838 | -5.17000 | 2.92644 |
| H | 2.10674 | -4.45331 | 4.50994 |
| C | 0.05104 | -0.90756 | 1.02046 |
| H | 0.62754 | 0.02134 | 1.05023 |
| C | -4.45607 | -0.24836 | 0.18553 |
| C | -5.62803 | -0.08235 | -0.54036 |
| C | -5.68768 | -0.39610 | -1.90336 |
| C | -4.57031 | -0.87164 | -2.58025 |
| C | -3.39076 | -1.03209 | -1.86171 |
| C | -3.34406 | -0.73210 | -0.49549 |
| H | -4.39616 | 0.00341 | 1.23883 |

| | | | |
|---|----------|----------|----------|
| H | -6.51121 | 0.30107 | -0.04166 |
| H | -6.61721 | -0.25709 | -2.44385 |
| H | -4.61229 | -1.09699 | -3.64034 |

SCF = -1520.57674162
H(0 K) = -1520.078237
H(298 K) = -1520.049155
G(298 K) = -1520.140220
SCF (BS2) = -1520.94925455
SCF(DCM) = -1520.59859437
Lowest Frequency = 19.4021cm⁻¹

62
TS2trans

| | | | |
|---|----------|----------|----------|
| C | 1.95842 | 2.01022 | -0.70946 |
| C | 0.59788 | 1.99724 | -0.65784 |
| C | 0.73481 | -0.90157 | -1.29774 |
| H | 2.58700 | 2.71027 | -0.17441 |
| C | 5.71589 | -0.81226 | -1.39655 |
| H | 6.16278 | -1.79253 | -1.32904 |
| C | 5.22659 | 1.40017 | -1.54209 |
| H | 5.32419 | 2.47200 | -1.63174 |
| C | 6.28146 | 0.43988 | -1.51265 |
| H | 7.34116 | 0.64638 | -1.55825 |
| N | 4.36158 | -0.63352 | -1.34228 |
| C | 4.05075 | 0.69489 | -1.43830 |
| C | 3.19985 | -1.50486 | -1.28696 |
| H | 2.96417 | -1.92183 | -2.27251 |
| H | 3.34542 | -2.31917 | -0.57122 |
| O | 0.47226 | -1.33599 | -2.40148 |
| O | -0.08774 | 1.05501 | -1.24659 |
| C | -0.19449 | 2.95627 | 0.18135 |
| C | -1.55709 | 2.69564 | 0.37176 |
| C | 0.36050 | 4.07547 | 0.81265 |
| C | -2.33672 | 3.50884 | 1.19064 |
| H | -1.98588 | 1.85050 | -0.15990 |
| C | -0.41730 | 4.89106 | 1.62698 |
| H | 1.40705 | 4.31683 | 0.65612 |
| C | -1.76839 | 4.60867 | 1.82736 |
| H | -3.39398 | 3.29163 | 1.31992 |
| H | 0.03182 | 5.75592 | 2.10597 |
| H | -2.37260 | 5.24832 | 2.46301 |
| C | -1.69756 | -0.60066 | 1.56989 |
| C | -1.52163 | -1.18244 | -0.65271 |
| H | -1.91835 | -1.38524 | 2.30004 |
| H | -1.99057 | 0.37787 | 1.95920 |
| N | -0.25589 | -1.20280 | -0.24545 |
| N | -2.38701 | -0.87423 | 0.31213 |
| S | -2.24524 | -1.43685 | -2.19236 |
| C | 2.56125 | 0.86702 | -1.45663 |
| C | 2.11113 | -0.50953 | -0.84323 |
| H | 2.16195 | -0.40094 | 0.24132 |
| H | 2.19227 | 0.86295 | -2.49537 |
| C | 0.68085 | -1.39925 | 2.06616 |
| C | 1.58165 | -0.71426 | 2.88040 |
| C | 0.59482 | -2.79032 | 2.14710 |
| C | 2.38409 | -1.41289 | 3.77889 |
| H | 1.66520 | 0.36649 | 2.79092 |
| C | 1.39947 | -3.48781 | 3.04153 |
| H | -0.09172 | -3.32604 | 1.49573 |
| C | 2.29253 | -2.79905 | 3.86075 |

| | | | |
|---|----------|----------|----------|
| H | 3.08760 | -0.87401 | 4.40470 |
| H | 1.33462 | -4.56965 | 3.09654 |
| H | 2.92213 | -3.34542 | 4.55537 |
| C | -0.20385 | -0.62087 | 1.12485 |
| H | 0.15391 | 0.40736 | 1.02442 |
| C | -4.82638 | -0.52448 | 0.69565 |
| C | -6.06895 | -0.53051 | 0.07292 |
| C | -6.19464 | -0.83156 | -1.28694 |
| C | -5.07827 | -1.13070 | -2.06208 |
| C | -3.83105 | -1.12881 | -1.44853 |
| C | -3.71659 | -0.82924 | -0.08460 |
| H | -4.71813 | -0.28906 | 1.74901 |
| H | -6.95408 | -0.29437 | 0.65296 |
| H | -7.17605 | -0.82844 | -1.74782 |
| H | -5.17713 | -1.35441 | -3.11891 |

SCF = -1520.57135201
H(0 K) = -1520.073917
H(298 K) = -1520.045621
G(298 K) = -1520.134353
SCF (BS2) = -1520.94210845
SCF(DCM) = -1520.59488561
Lowest Frequency = -68.3535cm⁻¹

62

47trans

| | | | |
|---|----------|----------|----------|
| C | -2.94071 | 0.35191 | -1.27278 |
| C | -2.19497 | -0.76335 | -1.21612 |
| C | -0.05254 | 0.50499 | -1.08025 |
| H | -4.01977 | 0.29193 | -1.33976 |
| C | -2.20353 | 4.84800 | 0.27776 |
| H | -1.54984 | 5.54794 | 0.77594 |
| C | -3.91405 | 3.71057 | -0.69056 |
| H | -4.88995 | 3.45263 | -1.07453 |
| C | -3.54299 | 4.92587 | -0.04119 |
| H | -4.19184 | 5.76147 | 0.17894 |
| N | -1.76117 | 3.62645 | -0.14333 |
| C | -2.78371 | 2.92975 | -0.73515 |
| C | -0.48239 | 2.91876 | -0.15610 |
| H | 0.14960 | 3.24452 | -0.99035 |
| H | 0.05051 | 3.05444 | 0.78970 |
| O | 0.56991 | 0.88764 | -2.09994 |
| O | -0.82735 | -0.77190 | -1.20658 |
| C | -2.74712 | -2.13699 | -1.15618 |
| C | -1.98731 | -3.21917 | -1.61410 |
| C | -4.00726 | -2.38410 | -0.59778 |
| C | -2.48863 | -4.51541 | -1.53687 |
| H | -1.00743 | -3.02614 | -2.03724 |
| C | -4.50647 | -3.67939 | -0.52499 |
| H | -4.58322 | -1.55554 | -0.19683 |
| C | -3.74939 | -4.75094 | -0.99520 |
| H | -1.89240 | -5.34532 | -1.90366 |
| H | -5.48432 | -3.85439 | -0.08694 |
| H | -4.13774 | -5.76239 | -0.93193 |
| C | 2.25160 | -1.28012 | 1.60642 |
| C | 2.28167 | -0.00290 | -0.30298 |
| H | 2.38962 | -0.69521 | 2.52338 |
| H | 2.50145 | -2.32431 | 1.80140 |
| N | 1.01536 | -0.04828 | -0.00110 |
| N | 3.06602 | -0.72527 | 0.52668 |
| S | 3.15566 | 0.81697 | -1.55419 |

| | | | |
|---|----------|----------|----------|
| C | -2.20982 | 1.65593 | -1.28264 |
| C | -0.97435 | 1.48904 | -0.37620 |
| H | -1.32837 | 1.08398 | 0.57717 |
| H | -1.83642 | 1.85340 | -2.30138 |
| C | -0.26271 | -0.79526 | 2.00444 |
| C | -1.44746 | -1.52790 | 1.97127 |
| C | -0.13829 | 0.27469 | 2.89399 |
| C | -2.50129 | -1.19685 | 2.81894 |
| H | -1.55773 | -2.33834 | 1.25530 |
| C | -1.18891 | 0.60378 | 3.74271 |
| H | 0.76868 | 0.87517 | 2.90042 |
| C | -2.37313 | -0.13201 | 3.70506 |
| H | -3.42413 | -1.76603 | 2.77238 |
| H | -1.09156 | 1.44183 | 4.42501 |
| H | -3.19657 | 0.13387 | 4.35970 |
| C | 0.82426 | -1.11628 | 1.01263 |
| H | 0.54324 | -2.02013 | 0.46050 |
| C | 5.47154 | -1.11995 | 1.05872 |
| C | 6.77352 | -0.83592 | 0.65509 |
| C | 7.02291 | -0.02671 | -0.45445 |
| C | 5.97320 | 0.52331 | -1.18822 |
| C | 4.67138 | 0.25499 | -0.78869 |
| C | 4.43147 | -0.56639 | 0.32283 |
| H | 5.26958 | -1.75202 | 1.91707 |
| H | 7.60454 | -1.25365 | 1.21290 |
| H | 8.04541 | 0.17978 | -0.75039 |
| H | 6.16899 | 1.15326 | -2.04985 |

SCF = -1520.58188595
H(0 K) = -1520.083323
H(298 K) = -1520.054704
G(298 K) = -1520.144561
SCF (BS2) = -1520.94910779
SCF(DCM) = -1520.60334642
Lowest Frequency = 13.1829cm⁻¹

62

TS3trans

| | | | |
|---|----------|----------|----------|
| C | -2.97992 | 0.33970 | -1.24492 |
| C | -2.17993 | -0.73778 | -1.27927 |
| C | -0.09737 | 0.61011 | -1.17959 |
| H | -4.05707 | 0.23333 | -1.22473 |
| C | -2.35552 | 4.80932 | 0.41820 |
| H | -1.70937 | 5.51726 | 0.91486 |
| C | -4.05962 | 3.63873 | -0.52156 |
| H | -5.03985 | 3.35491 | -0.87488 |
| C | -3.70927 | 4.84422 | 0.15655 |
| H | -4.38006 | 5.64504 | 0.43262 |
| N | -1.88382 | 3.62225 | -0.06456 |
| C | -2.90258 | 2.90619 | -0.63982 |
| C | -0.57907 | 2.96934 | -0.15622 |
| H | 0.00508 | 3.35107 | -1.00134 |
| H | -0.01183 | 3.09145 | 0.77108 |
| O | 0.56227 | 1.04261 | -2.13948 |
| O | -0.81514 | -0.66623 | -1.38464 |
| C | -2.64844 | -2.14111 | -1.21891 |
| C | -1.84563 | -3.17215 | -1.71862 |
| C | -3.86650 | -2.46774 | -0.61003 |
| C | -2.26133 | -4.49772 | -1.62582 |
| H | -0.89921 | -2.91807 | -2.18352 |
| C | -4.28040 | -3.79148 | -0.52239 |

H -4.47402 -1.67992 -0.17530
 C -3.47900 -4.81308 -1.02964
 H -1.63130 -5.28694 -2.02436
 H -5.22554 -4.02822 -0.04358
 H -3.80026 -5.84701 -0.95481
 C 2.22427 -1.36790 1.49260
 C 2.26980 0.06695 -0.29913
 H 2.34673 -0.86432 2.45911
 H 2.47120 -2.42552 1.60072
 N 1.00214 -0.00938 -0.03331
 N 3.05236 -0.72306 0.47663
 S 3.17132 1.00335 -1.45377
 C -2.30581 1.67452 -1.25449
 C -1.02363 1.53055 -0.40901
 H -1.32038 1.07436 0.54026
 H -1.99433 1.91472 -2.28512
 C -0.27936 -0.89201 1.91289
 C -1.41936 -1.69243 1.91895
 C -0.18102 0.17453 2.81046
 C -2.45653 -1.42964 2.81113
 H -1.50809 -2.50731 1.20513
 C -1.21447 0.43639 3.70177
 H 0.69408 0.82072 2.78878
 C -2.35532 -0.36670 3.70236
 H -3.34572 -2.05173 2.79587
 H -1.13844 1.27267 4.38893
 H -3.16563 -0.15515 4.39234
 C 0.80318 -1.14752 0.89658
 H 0.51454 -2.00860 0.28198
 C 5.44994 -1.12950 1.03194
 C 6.75709 -0.79340 0.68782
 C 7.02110 0.11370 -0.33901
 C 5.98013 0.71293 -1.04717
 C 4.67413 0.39258 -0.70510
 C 4.41802 -0.52764 0.32268
 H 5.23886 -1.83868 1.82536
 H 7.58048 -1.24859 1.22734
 H 8.04702 0.35902 -0.59001
 H 6.18463 1.42043 -1.84408

SCF = -1520.58188254
 H(0 K) = -1520.084034
 H(298 K) = -1520.055973
 G(298 K) = -1520.144178
 SCF (BS2) = -1520.94908942
 SCF(DCM) = -1520.60204523
 Lowest Frequency = -91.6091cm⁻¹

32

2l_{trans}

C 0.08494 -0.81464 -0.33381
 C 1.09250 0.06517 -0.26337
 C -0.35892 2.00743 -0.20634
 H 0.26181 -1.87545 -0.21299
 C -4.64993 -0.50955 0.52529
 H -5.47660 0.08564 0.88203
 C -3.21971 -2.13200 -0.17064
 H -2.81418 -3.09173 -0.45428
 C -4.54581 -1.86217 0.27950
 H -5.33408 -2.58707 0.42039
 N -3.43091 0.04318 0.25409

C -2.55741 -0.92892 -0.17123
 C -2.86809 1.39153 0.25983
 H -3.13984 1.94731 -0.64491
 H -3.18834 1.95772 1.13597
 O -0.50910 3.17632 -0.41253
 O 0.87264 1.43523 -0.40823
 C 2.52304 -0.23892 -0.06545
 C 3.39780 0.74898 0.39814
 C 3.02067 -1.51962 -0.33157
 C 4.73950 0.45101 0.61344
 H 3.01986 1.74784 0.58390
 C 4.36001 -1.81357 -0.11218
 H 2.36215 -2.28245 -0.73412
 C 5.22398 -0.82937 0.36423
 H 5.40850 1.22452 0.97629
 H 4.73375 -2.80972 -0.32557
 H 6.27160 -1.05802 0.53069
 C -1.28149 -0.25153 -0.56963
 C -1.38359 1.03095 0.27784
 H -1.10343 0.74481 1.30062
 H -1.35812 0.03316 -1.63489

SCF = -822.378729697
 H(0 K) = -822.120657
 H(298 K) = -822.106600
 G(298 K) = -822.162684
 SCF (BS2) = -822.589593582
 SCF(DCM) = -822.388190986
 Lowest Frequency = 35.9039cm⁻¹

(c) 2l_{trans} formation from (E)-45

62

(E)-45

C 1.24291 2.47282 -0.53495
 C 1.90380 1.24404 -0.98315
 C -2.15343 0.68838 1.30496
 H 1.81439 3.23388 -0.01547
 C -2.80689 4.84985 -0.12026
 H -3.87525 4.97292 -0.01064
 C -0.57762 5.06571 -0.18114
 H 0.42510 5.46946 -0.18463
 C -1.77626 5.76760 0.02150
 H -1.89113 6.81970 0.23452
 N -2.28503 3.63887 -0.42414
 C -0.90660 3.73797 -0.44956
 C -3.05306 2.37112 -0.40978
 H -4.07379 2.65738 -0.68558
 H -2.66696 1.76239 -1.22945
 O -1.80600 0.27985 2.42968
 O 1.34967 0.43594 -1.72928
 C 3.29321 0.94768 -0.50520
 C 4.06960 0.06032 -1.25438
 C 3.79882 1.46894 0.68925
 C 5.34868 -0.27921 -0.83235
 H 3.64305 -0.35846 -2.16008
 C 5.07101 1.10765 1.12426
 H 3.18841 2.13144 1.29539
 C 5.85015 0.24162 0.35961
 H 5.95125 -0.96141 -1.42409
 H 5.45587 1.50513 2.05800

| | | | |
|---|----------|----------|----------|
| H | 6.84673 | -0.02944 | 0.69426 |
| C | -0.90492 | -1.55193 | -1.59709 |
| C | -0.37679 | -0.76395 | 0.47690 |
| H | -1.16351 | -2.53218 | -2.00089 |
| H | -0.42155 | -0.91908 | -2.34787 |
| N | -1.49676 | -0.12885 | 0.19236 |
| N | -0.01090 | -1.66351 | -0.44690 |
| S | 0.73041 | -0.60974 | 1.78940 |
| C | -0.08193 | 2.61241 | -0.76530 |
| C | -2.99768 | 1.68592 | 0.91074 |
| H | -3.48242 | 2.19872 | 1.73459 |
| H | -0.56053 | 1.76224 | -1.24661 |
| C | -3.17367 | -1.85417 | -0.46282 |
| C | -3.98116 | -2.45983 | -1.42908 |
| C | -3.31268 | -2.21378 | 0.87739 |
| C | -4.91178 | -3.42577 | -1.06629 |
| H | -3.88205 | -2.16967 | -2.47348 |
| C | -4.25058 | -3.18091 | 1.23617 |
| H | -2.71938 | -1.72379 | 1.64606 |
| C | -5.04598 | -3.79045 | 0.27197 |
| H | -5.53587 | -3.88784 | -1.82453 |
| H | -4.36016 | -3.45102 | 2.28143 |
| H | -5.77431 | -4.54148 | 0.56073 |
| C | -2.13098 | -0.85518 | -0.93333 |
| H | -2.58319 | -0.15345 | -1.63625 |
| C | 1.97289 | -3.02256 | -1.11995 |
| C | 3.25148 | -3.41060 | -0.73104 |
| C | 3.81494 | -2.95289 | 0.46266 |
| C | 3.11479 | -2.08602 | 1.29672 |
| C | 1.84135 | -1.69062 | 0.91175 |
| C | 1.27646 | -2.16131 | -0.28147 |
| H | 1.53146 | -3.37203 | -2.04699 |
| H | 3.81976 | -4.07815 | -1.36988 |
| H | 4.81838 | -3.25954 | 0.73693 |
| H | 3.56008 | -1.70890 | 2.21141 |

SCF = -1520.57325400
H(0 K) = -1520.076605
H(298 K) = -1520.047010
G(298 K) = -1520.137365
SCF (BS2) = -1520.94469465
SCF(DCM) = -1520.59386756
Lowest Frequency = 24.2393cm⁻¹

62

TS1trans (E)

| | | | |
|---|----------|---------|----------|
| C | 0.12782 | 2.70550 | -0.31183 |
| C | 1.15672 | 1.77236 | -0.62630 |
| C | -1.02459 | 0.46146 | 1.51133 |
| H | 0.34886 | 3.66185 | 0.14396 |
| C | -4.62962 | 3.29287 | -0.47953 |
| H | -5.62662 | 3.02104 | -0.16548 |
| C | -2.74607 | 4.27350 | -1.25768 |
| H | -2.05812 | 4.94902 | -1.74416 |
| C | -4.16083 | 4.39945 | -1.15422 |
| H | -4.76608 | 5.21650 | -1.51907 |
| N | -3.55368 | 2.50396 | -0.18367 |
| C | -2.40264 | 3.08928 | -0.64384 |
| C | -3.42875 | 1.28216 | 0.61542 |
| H | -4.20625 | 1.29751 | 1.38816 |
| H | -3.60496 | 0.39029 | 0.00319 |

| | | | |
|---|----------|----------|----------|
| O | -0.10666 | 0.69283 | 2.30039 |
| O | 0.95120 | 0.67749 | -1.20924 |
| C | 2.57877 | 2.06084 | -0.22609 |
| C | 3.59366 | 1.31196 | -0.83021 |
| C | 2.91512 | 2.96477 | 0.78488 |
| C | 4.92056 | 1.47947 | -0.45097 |
| H | 3.30972 | 0.59238 | -1.59226 |
| C | 4.24287 | 3.13029 | 1.16952 |
| H | 2.13252 | 3.51248 | 1.29893 |
| C | 5.24937 | 2.39156 | 0.55096 |
| H | 5.69947 | 0.89668 | -0.93475 |
| H | 4.49130 | 3.82991 | 1.96160 |
| H | 6.28434 | 2.52387 | 0.85159 |
| C | -0.46112 | -1.90629 | -1.34446 |
| C | 0.45378 | -1.19714 | 0.63553 |
| H | -0.77697 | -2.89162 | -1.69180 |
| H | -0.15451 | -1.25967 | -2.17082 |
| N | -0.79184 | -0.72849 | 0.69926 |
| N | 0.65728 | -2.00073 | -0.40993 |
| S | 1.86432 | -0.84846 | 1.55228 |
| C | -1.18419 | 2.27190 | -0.49622 |
| C | -2.04361 | 1.38307 | 1.19606 |
| H | -1.96326 | 2.21559 | 1.89055 |
| H | -1.21074 | 1.36610 | -1.10157 |
| C | -2.67538 | -2.16381 | -0.06891 |
| C | -3.74460 | -2.32646 | -0.95251 |
| C | -2.64788 | -2.89408 | 1.11789 |
| C | -4.77273 | -3.21510 | -0.65821 |
| H | -3.77416 | -1.74573 | -1.87202 |
| C | -3.67987 | -3.78212 | 1.41333 |
| H | -1.82876 | -2.75599 | 1.81751 |
| C | -4.74085 | -3.94575 | 0.52740 |
| H | -5.60158 | -3.32984 | -1.34891 |
| H | -3.65562 | -4.34388 | 2.34137 |
| H | -5.54496 | -4.63511 | 0.76287 |
| C | -1.55397 | -1.22726 | -0.46318 |
| H | -1.96158 | -0.37561 | -1.00824 |
| C | 2.52788 | -3.02061 | -1.70371 |
| C | 3.90588 | -3.20254 | -1.73020 |
| C | 4.72198 | -2.69441 | -0.71434 |
| C | 4.17984 | -1.98484 | 0.35262 |
| C | 2.80307 | -1.79805 | 0.38405 |
| C | 1.99408 | -2.30947 | -0.63534 |
| H | 1.88885 | -3.40641 | -2.49060 |
| H | 4.35426 | -3.74421 | -2.55579 |
| H | 5.79457 | -2.84661 | -0.76225 |
| H | 4.81429 | -1.56406 | 1.12543 |

SCF = -1520.54661810
H(0 K) = -1520.050310
H(298 K) = -1520.021473
G(298 K) = -1520.111245
SCF (BS2) = -1520.91858389
SCF(DCM) = -1520.56635786
Lowest Frequency = -356.3296cm⁻¹

62

46trans (E)

| | | | |
|---|----------|---------|----------|
| C | 0.18534 | 2.55335 | -0.02914 |
| C | 1.15529 | 1.67951 | -0.46540 |
| C | -1.11950 | 0.35232 | 1.56872 |

| | | | |
|---|----------|----------|----------|
| H | 0.41504 | 3.49342 | 0.45658 |
| C | -4.54497 | 3.48247 | -0.47597 |
| H | -5.56438 | 3.31041 | -0.16510 |
| C | -2.57774 | 4.24080 | -1.32560 |
| H | -1.84336 | 4.82594 | -1.85811 |
| C | -3.98550 | 4.47070 | -1.25610 |
| H | -4.52677 | 5.28454 | -1.71713 |
| N | -3.51954 | 2.67178 | -0.06767 |
| C | -2.32571 | 3.11655 | -0.57947 |
| C | -3.41029 | 1.46104 | 0.73114 |
| H | -4.05023 | 1.50608 | 1.61592 |
| H | -3.68682 | 0.56941 | 0.15168 |
| O | -0.53548 | 0.34335 | 2.62619 |
| O | 0.91892 | 0.56958 | -1.08009 |
| C | 2.61250 | 1.96863 | -0.19421 |
| C | 3.56613 | 1.20291 | -0.87272 |
| C | 3.06093 | 2.90405 | 0.74570 |
| C | 4.92704 | 1.37584 | -0.63585 |
| H | 3.20162 | 0.46505 | -1.58094 |
| C | 4.42022 | 3.07889 | 0.98569 |
| H | 2.34050 | 3.48405 | 1.31333 |
| C | 5.36142 | 2.31585 | 0.29554 |
| H | 5.65006 | 0.77221 | -1.17861 |
| H | 4.74815 | 3.80772 | 1.72123 |
| H | 6.42175 | 2.45345 | 0.48533 |
| C | -0.44456 | -1.83703 | -1.38391 |
| C | 0.40265 | -1.22462 | 0.65220 |
| H | -0.76446 | -2.79840 | -1.78906 |
| H | -0.07481 | -1.15003 | -2.14810 |
| N | -0.84396 | -0.73177 | 0.68261 |
| N | 0.62687 | -2.00725 | -0.39856 |
| S | 1.76137 | -0.94906 | 1.66172 |
| C | -1.23557 | 2.14790 | -0.21493 |
| C | -1.90929 | 1.52862 | 1.07069 |
| H | -1.79024 | 2.26317 | 1.87214 |
| H | -1.19647 | 1.37935 | -0.99704 |
| C | -2.70279 | -2.11581 | -0.19011 |
| C | -3.84168 | -2.11976 | -0.99710 |
| C | -2.61128 | -3.01550 | 0.87289 |
| C | -4.87595 | -3.01803 | -0.75025 |
| H | -3.92017 | -1.41235 | -1.81955 |
| C | -3.64709 | -3.91083 | 1.12112 |
| H | -1.73536 | -3.00852 | 1.51577 |
| C | -4.77898 | -3.91584 | 0.30918 |
| H | -5.75932 | -3.01046 | -1.38008 |
| H | -3.57102 | -4.60426 | 1.95218 |
| H | -5.58603 | -4.61367 | 0.50631 |
| C | -1.56820 | -1.17437 | -0.53055 |
| H | -1.95360 | -0.30310 | -1.05968 |
| C | 2.55769 | -2.90180 | -1.69666 |
| C | 3.94099 | -3.03708 | -1.70340 |
| C | 4.72115 | -2.55487 | -0.64737 |
| C | 4.13782 | -1.91750 | 0.44272 |
| C | 2.75638 | -1.77563 | 0.44937 |
| C | 1.98033 | -2.26142 | -0.60719 |
| H | 1.94702 | -3.26360 | -2.51664 |
| H | 4.42244 | -3.52022 | -2.54635 |
| H | 5.79922 | -2.66522 | -0.68333 |
| H | 4.74354 | -1.50874 | 1.24403 |

SCF = -1520.56352307

H(0 K) = -1520.065397
H(298 K) = -1520.036365
G(298 K) = -1520.127014
SCF (BS2) = -1520.93664723
SCF(DCM) = -1520.58564372
Lowest Frequency = 16.2203cm⁻¹

62
TS2trans(E)

| | | | |
|---|----------|----------|----------|
| C | -1.45129 | 2.62062 | -0.22329 |
| C | -0.10765 | 2.44183 | -0.41786 |
| C | -0.57183 | -0.04491 | 1.45960 |
| H | -1.91523 | 3.58419 | -0.05740 |
| C | -5.55928 | 0.44656 | 0.93596 |
| H | -6.10349 | -0.26865 | 1.53381 |
| C | -4.84387 | 2.14500 | -0.39225 |
| H | -4.82831 | 3.00533 | -1.04445 |
| C | -5.99132 | 1.50218 | 0.16198 |
| H | -7.02232 | 1.79369 | 0.02158 |
| N | -4.19286 | 0.43912 | 0.87000 |
| C | -3.74730 | 1.45724 | 0.06915 |
| C | -3.13424 | -0.38895 | 1.42071 |
| H | -3.31588 | -0.62420 | 2.47281 |
| H | -3.03090 | -1.32764 | 0.86191 |
| O | 0.04865 | 0.16048 | 2.48154 |
| O | 0.42954 | 1.26224 | -0.46332 |
| C | 0.82004 | 3.61644 | -0.53003 |
| C | 2.18409 | 3.40674 | -0.30986 |
| C | 0.38728 | 4.90521 | -0.85861 |
| C | 3.09058 | 4.45879 | -0.38942 |
| H | 2.50266 | 2.39547 | -0.07861 |
| C | 1.29147 | 5.95885 | -0.94116 |
| H | -0.66329 | 5.07705 | -1.07191 |
| C | 2.64753 | 5.74156 | -0.70305 |
| H | 4.14684 | 4.27956 | -0.20831 |
| H | 0.93916 | 6.95264 | -1.20178 |
| H | 3.35293 | 6.56430 | -0.77016 |
| C | 0.94521 | -1.56270 | -1.54958 |
| C | 1.31805 | -1.21794 | 0.68855 |
| H | 0.94690 | -2.46917 | -2.15709 |
| H | 1.21238 | -0.67566 | -2.13086 |
| N | 0.00277 | -1.02799 | 0.57912 |
| N | 1.87980 | -1.67488 | -0.42891 |
| S | 2.42918 | -0.92301 | 1.96689 |
| C | -2.25489 | 1.37450 | -0.07758 |
| C | -1.92955 | 0.56056 | 1.23093 |
| H | -1.98169 | 1.30068 | 2.03411 |
| H | -2.06699 | 0.72948 | -0.94637 |
| C | -1.34146 | -2.52970 | -0.87114 |
| C | -2.55164 | -2.42717 | -1.55663 |
| C | -1.00420 | -3.73198 | -0.24457 |
| C | -3.41830 | -3.51685 | -1.61537 |
| H | -2.82606 | -1.48575 | -2.02673 |
| C | -1.86778 | -4.81924 | -0.30379 |
| H | -0.06679 | -3.81163 | 0.30247 |
| C | -3.07700 | -4.71199 | -0.99023 |
| H | -4.36286 | -3.42563 | -2.14120 |
| H | -1.60246 | -5.74880 | 0.18916 |
| H | -3.75363 | -5.55925 | -1.03103 |
| C | -0.40915 | -1.34572 | -0.81947 |
| H | -0.85284 | -0.44481 | -1.22772 |

```

C    4.11560 -2.23144 -1.38458
C    5.47130 -2.30695 -1.09049
C    5.95648 -1.97853  0.18001
C    5.09702 -1.55722  1.18903
C    3.73898 -1.47636  0.90194
C    3.26067 -1.81519 -0.36938
H    3.73191 -2.48258 -2.36743
H    6.16385 -2.62587 -1.86149
H    7.01944 -2.04801  0.38174
H    5.47504 -1.29133  2.17037

SCF    =          -1520.55751594
H(0 K)=          -1520.059843
H(298 K)=        -1520.031394
G(298 K)=        -1520.120697
SCF (BS2) =      -1520.92592421
SCF (DCM) =      -1520.58229559
Lowest Frequency = -20.9358cm-1

```

1.6.2 B3LYP

(a) Formation of 21cis from (Z)-45

```

62
(Z)-45
H    5.70560 -0.98093 -0.63739
C    5.32337 -3.02326 -1.43373
C    5.01111 -1.73387 -0.98401
H    6.30283 -3.47355 -1.51263
H    5.30154  5.29129  0.27225
H    3.83866  6.68609  1.71790
C    3.53308  5.68046  1.44273
C    4.35725  4.89515  0.63479
H    4.61023  3.01132 -0.36058
C    3.96922  3.60143  0.28574
C    2.74758  3.07664  0.73581
C    1.92103  3.88305  1.53377
C    2.31109  5.17054  1.89103
H    1.66457  5.77989  2.51656
H    0.97195  3.47304  1.86160
H    3.92092 -4.63020 -2.13038
O    1.06199  1.42395  0.52999
H    4.29579  0.94570 -0.00727
C    3.23931  0.72252 -0.11145
C    2.26597  1.69736  0.37530
C    2.81550 -0.46303 -0.63271
H    1.74489 -0.59397 -0.72537
C    3.61644 -1.57493 -1.03621
C    4.11568 -3.63716 -1.75038
N    3.08723 -2.78036 -1.51453
C    1.67652 -3.14183 -1.85826
C    0.63999 -2.62898 -0.91813
H    0.74886 -2.80700  0.14381
H    1.45087 -2.76366 -2.86098
O   -0.76908 -1.64772 -2.59940
C   -0.39977 -1.88881 -1.42040
S   -2.71552  0.08183 -2.41508
C   -3.72494  1.37404 -1.66723
C   -3.49668  1.48149 -0.28153
C   -4.14446  2.44517  0.48938
N   -2.58444  0.51877  0.14309

```

```

C   -2.10385 -0.27426 -0.83464
N   -1.22841 -1.16641 -0.41449
C   -0.97788 -0.97389  1.04317
H   -2.55176  0.07714  2.21586
C   -1.85898  0.28136  1.39610
H   -1.22954  1.14449  1.62773
H    1.69937 -4.23859 -1.92192
H    0.07244 -0.70094  1.16126
C   -1.31254 -2.19557  1.87670
C   -0.53404 -2.48764  3.00296
C   -0.85647 -3.56730  3.82712
C   -1.95859 -4.36934  3.52846
C   -2.73494 -4.08803  2.40175
C   -2.41571 -3.00633  1.58159
H    0.33217 -1.87135  3.23134
H   -0.24139 -3.78532  4.69535
H   -2.20709 -5.21373  4.16473
H   -3.58742 -4.71532  2.15774
H   -3.01266 -2.80451  0.69681
H   -3.96008  2.52299  1.55586
C   -5.03493  3.30610 -0.15553
H   -5.55078  4.06564  0.42341
C   -5.27054  3.20385 -1.53115
H   -5.96850  3.88279 -2.01052
C   -4.61438  2.23704 -2.29928
H   -4.79379  2.16384 -3.36769

```

```

SCF    =          -1521.21710428
H(0 K)=          -1520.726982
H(298 K)=        -1520.696072
G(298 K)=        -1520.793768
SCF (BS2) =      -1521.58304195
SCF (DCM) =      -1521.23456151
Lowest Frequency =  9.3588cm-1

```

```

62
TS1cis
H   -3.40121 -4.44567  0.83463
C   -5.02655 -3.85477 -0.60690
C   -3.84909 -3.70944  0.18253
H   -5.64960 -4.73602 -0.68217
H    3.45357 -4.41237 -0.69211
H    4.94622 -4.17026  1.28358
C    3.96708 -3.69873  1.27758
C    3.12724 -3.83560  0.16966
H    1.23445 -3.34447 -0.71273
C    1.86719 -3.23562  0.16211
C    1.42148 -2.48353  1.26184
C    2.28097 -2.34660  2.36367
C    3.53671 -2.95120  2.37667
H    4.18116 -2.84269  3.24566
H    1.92740 -1.75917  3.20460
H   -6.00282 -2.36109 -1.97276
O   -0.05587 -0.87637  2.20205
H   -0.76494 -2.95883 -0.30166
C   -0.93972 -2.18308  0.43350
C    0.07899 -1.78755  1.32176
C   -2.25255 -1.61366  0.51318
H   -2.42552 -1.15128  1.48739
C   -3.38861 -2.41879 -0.01129
C   -5.24146 -2.65816 -1.26615

```

```

N   -4.24373  -1.79578  -0.88304
C   -3.86683  -0.47584  -1.37322
C   -2.69184  -0.02142  -0.51948
H   -2.95283   0.68491   0.26311
H   -3.57548  -0.53253  -2.42761
O   -1.14053  -0.09556  -2.34844
C   -1.48769   0.30237  -1.23428
S    1.54028   0.34997  -2.32626
C    3.12879   0.81863  -1.64112
C    2.99367   1.38409  -0.35940
C    4.10437   1.80881   0.36828
N    1.65361   1.43874   0.01674
C    0.79905   0.93885  -0.88163
N   -0.47397   1.00008  -0.48790
C   -0.55530   1.62678   0.87299
H    1.18589   2.86420   1.50977
C    0.95441   1.82782   1.25279
H    1.22318   1.13791   2.05543
H   -4.71507   0.21319  -1.28506
H   -0.94521   0.86755   1.55694
C   -1.37431   2.90003   0.88736
C   -2.19082   3.16389   1.99426
C   -2.91702   4.35374   2.07190
C   -2.83978   5.28834   1.03866
C   -2.03296   5.02913  -0.07207
C   -1.30213   3.84380  -0.14652
H   -2.25799   2.43263   2.79571
H   -3.54820   4.54436   2.93483
H   -3.40932   6.21131   1.09434
H   -1.97479   5.74977  -0.88259
H   -0.68631   3.64704  -1.02015
H    3.99233   2.23478   1.35952
C    5.36016   1.65657  -0.21843
H    6.24203   1.97534   0.32773
C    5.50157   1.09648  -1.49493
H    6.49065   0.98774  -1.92777
C    4.38643   0.66958  -2.21895
H    4.49883   0.22867  -3.20437

SCF   =          -1521.19590092
H(0 K)=          -1520.705475
H(298 K)=        -1520.675799
G(298 K)=        -1520.770339
SCF (BS2) =      -1521.56152638
SCF (DCM) =      -1521.21664124
Lowest Frequency = -293.6045cm-1

```

```

62
46cis
H   -3.69813  -5.43636  -1.05402
C   -2.87709  -4.72421  -1.06363
C   -2.56834  -4.01611  -2.22732
H   -3.14881  -4.17980  -3.13238
C   -1.06435  -3.59332   0.07923
H   -1.26297  -2.53508  -3.12479
C   -1.51656  -3.10033  -2.23405
H   -0.49678  -3.42553   0.98935
C   -0.73824  -2.87947  -1.08648
C   -2.12046  -4.50518   0.09080
H   -2.35487  -5.04537   1.00498
C    0.38199  -1.86544  -1.17436

```

```

O    0.31803  -1.03536  -2.16188
H    1.43274  -2.66912   0.52428
C   -1.13933   0.87784   0.82780
C   -3.32258   1.08592   0.15135
C   -3.49036   0.64670   1.47821
S   -1.91520   0.38143   2.28645
C    1.38148  -1.87676  -0.21359
C    1.16158   0.39659   1.30705
O    0.84065   0.12843   2.45411
C    2.57370  -0.95617  -0.32047
C    2.54499   0.27046   0.70931
H    2.57700  -0.55257  -1.33964
N    0.14943   0.93769   0.46692
C   -4.41909   1.33391  -0.67413
N   -1.97162   1.22020  -0.16079
C   -1.22768   1.40189  -1.42040
H   -1.55224   2.30629  -1.93728
H   -1.32801   0.50156  -2.03895
C    0.25493   1.48271  -0.93014
C    3.62029  -0.01448   1.78837
H    3.16597  -0.39816   2.70779
H    4.19855   0.88143   2.03870
C    5.63781  -1.63242   1.45887
H    6.22525  -1.33528   2.31514
C    5.85166  -2.60325   0.49630
N    4.44994  -1.01709   1.14504
C    3.90110  -1.57938   0.02068
C    4.75257  -2.57545  -0.41480
H    4.60716  -3.20685  -1.27969
H    6.71205  -3.25747   0.44653
H    2.78711   1.20126   0.18424
C    0.86867   2.86659  -0.96825
H    0.79412   0.74290  -1.53643
C    0.61850   3.83169   0.01727
C    1.16946   5.10905  -0.08800
C    1.97295   5.43922  -1.18152
C    2.22796   4.48402  -2.16672
C    1.68258   3.20397  -2.05827
H    0.00378   3.58538   0.87898
H    0.97271   5.84571   0.68552
H    2.40294   6.43326  -1.26099
H    2.85976   4.72984  -3.01507
H    1.89084   2.45749  -2.82031
H   -4.28200   1.66063  -1.69922
C   -5.69063   1.13799  -0.13843
H   -6.56100   1.31955  -0.76049
C   -5.86340   0.70830   1.18477
H   -6.86491   0.56320   1.57622
C   -4.76426   0.45616   2.00723
H   -4.89992   0.11381   3.02810

```

```

SCF   =          -1521.19901372
H(0 K)=          -1520.707279
H(298 K)=        -1520.677552
G(298 K)=        -1520.770951
SCF (BS2) =      -1521.56395238
SCF (DCM) =      -1521.22271082
Lowest Frequency = 15.3108cm-1

```

```

62
TS2cis

```

H 2.60408 6.55665 -0.84270
 C 1.96150 5.68020 -0.82937
 C 2.50569 4.40185 -0.96850
 H 3.57937 4.27931 -1.09290
 C -0.24791 4.69928 -0.67076
 H 2.07747 2.28077 -1.07409
 C 1.67579 3.28115 -0.95377
 H -1.32151 4.83073 -0.58135
 C 0.28715 3.40602 -0.79433
 C 0.57851 5.82180 -0.68388
 H 0.14116 6.81254 -0.58817
 C -0.55111 2.15666 -0.78484
 O 0.02510 1.04513 -1.11591
 H -2.35189 3.06306 0.01981
 C 1.41787 -0.92350 0.69672
 C 3.56431 -1.19011 -0.08650
 C 3.79959 -0.53317 1.13620
 S 2.26823 -0.13567 1.97497
 C -1.87293 2.18272 -0.38809
 C -0.82836 -0.23322 1.12269
 O -0.41556 0.38520 2.09245
 C -2.64176 0.90956 -0.44206
 C -2.24359 -0.24634 0.65471
 H -2.47743 0.43005 -1.41674
 N 0.11730 -1.07882 0.45000
 C 4.61550 -1.55012 -0.92943
 N 2.20181 -1.40192 -0.28153
 C 1.39562 -1.72973 -1.46596
 H 1.66943 -2.70596 -1.87011
 H 1.52645 -0.94120 -2.21227
 C -0.06291 -1.71130 -0.89669
 C -3.24275 -0.02332 1.81282
 H -2.84241 0.69269 2.53801
 H -3.48749 -0.95381 2.33584
 C -5.71983 0.71141 1.42167
 H -6.14768 0.36003 2.34903
 C -6.28448 1.38299 0.35185
 N -4.39709 0.51002 1.11146
 C -4.10430 1.04894 -0.11622
 C -5.26356 1.60231 -0.62294
 H -5.37198 2.10139 -1.57557
 H -7.32364 1.67328 0.27164
 H -2.46548 -1.20672 0.18101
 C -0.71721 -3.07550 -0.82591
 H -0.64001 -0.99831 -1.48579
 C -0.34045 -4.02790 0.13139
 C -0.92987 -5.29155 0.13965
 C -1.90015 -5.61975 -0.81065
 C -2.28195 -4.67707 -1.76570
 C -1.69469 -3.41042 -1.77096
 H 0.40460 -3.77723 0.88175
 H -0.63475 -6.01937 0.88984
 H -2.36022 -6.60338 -0.80130
 H -3.04240 -4.92150 -2.50128
 H -2.00071 -2.67367 -2.50924
 H 4.42743 -2.05122 -1.87304
 C 5.91210 -1.23998 -0.51994
 H 6.74748 -1.50609 -1.15945
 C 6.15238 -0.59187 0.69876
 H 7.17089 -0.36264 0.99454
 C 5.09722 -0.22988 1.53904

H 5.28436 0.28267 2.47724
 SCF = -1521.19600566
 H(0 K) = -1520.704596
 H(298 K) = -1520.675578
 G(298 K) = -1520.767003
 SCF (BS2) = -1521.56234363
 SCF (DCM) = -1521.21960278
 Lowest Frequency = -25.1674cm⁻¹

30
 24
 C -0.38716 -1.04090 -0.60999
 C 0.53487 1.05823 -0.53275
 H -0.63320 -1.46375 0.37309
 H -0.34930 -1.84876 -1.34544
 N -0.68184 1.38547 -0.74544
 N 0.86561 -0.29253 -0.55478
 S 1.96458 2.04383 -0.16412
 C -2.73018 -0.00609 -0.32939
 C -3.70166 -0.87667 -0.84020
 C -3.00823 0.70780 0.84149
 C -4.92385 -1.04191 -0.18784
 H -3.50316 -1.42435 -1.75921
 C -4.23304 0.54827 1.49159
 H -2.26571 1.40120 1.22261
 C -5.19235 -0.32911 0.98244
 H -5.66808 -1.71925 -0.59737
 H -4.43977 1.11433 2.39570
 H -6.14553 -0.45092 1.48907
 C -1.38688 0.11041 -1.02239
 H -1.55292 0.05110 -2.10741
 C 2.69482 -1.87263 0.07446
 C 4.02533 -1.96359 0.49527
 C 4.79099 -0.81738 0.71978
 C 4.23496 0.45495 0.53419
 C 2.91248 0.55139 0.12363
 C 2.14009 -0.60668 -0.11455
 H 2.10306 -2.76443 -0.10553
 H 4.46612 -2.94416 0.64716
 H 5.82276 -0.90733 1.04406
 H 4.82494 1.34800 0.71619

SCF = -698.524932235
 H(0 K) = -698.289372
 H(298 K) = -698.275635
 G(298 K) = -698.331954
 SCF (DCM) = -698.532436265
 SCF (BS2) = -698.678554617
 Lowest Frequency = 19.5982cm⁻¹

32
 21cis
 H 5.89536 -1.56048 -0.59037
 C 4.89170 -1.19302 -0.39755
 C 4.65571 0.17650 -0.27267
 H 5.47684 0.88147 -0.36524
 C 2.53680 -1.61934 -0.04389
 H 3.18802 1.71579 0.06688
 C 3.36769 0.65136 -0.02833
 H 1.71286 -2.32387 0.00800

C 2.29163 -0.24270 0.10080
 C 3.82525 -2.08867 -0.28420
 H 3.99492 -3.15556 -0.39698
 C 0.93239 0.25933 0.38638
 O 0.81363 1.61420 0.05846
 H 0.08974 -1.45999 1.22826
 C -0.07664 -0.43074 0.93433
 C -0.37941 2.28034 0.11081
 O -0.38654 3.47143 -0.07231
 C -1.44944 0.15164 1.15880
 C -1.63171 1.45645 0.32777
 H -1.60174 0.34824 2.22871
 C -2.24947 0.98687 -1.02743
 H -1.47652 0.75104 -1.77032
 H -2.91818 1.74036 -1.45083
 C -3.90359 -1.03609 -1.17524
 H -4.36752 -0.81078 -2.12393
 C -4.09708 -2.08416 -0.29294
 N -2.96097 -0.21034 -0.61530
 C -2.54394 -0.71796 0.59113
 C -3.23439 -1.88826 0.82851
 H -3.14761 -2.52578 1.69717
 H -4.79755 -2.89673 -0.42950
 H -2.35167 2.11453 0.81830

SCF = -822.710561318
 H(0 K) = -822.455345
 H(298 K) = -822.441032
 G(298 K) = -822.498116
 SCF (BS2) = -822.921719275
 SCF (DCM) = -822.719298926
 Lowest Frequency = 35.4388cm⁻¹

(b) 21trans formation from (Z)-45

62
 TS1trans
 C 2.09691 1.39411 -0.48819
 C 0.82165 2.00547 -0.46904
 C 0.74522 -1.92316 -0.80654
 H 2.93138 1.83770 0.04292
 C 5.47467 -1.50746 -1.90703
 H 5.98228 -2.46093 -1.88293
 C 4.84051 0.66280 -2.07281
 H 4.83596 1.72603 -2.26636
 C 5.91955 -0.24735 -2.26527
 H 6.91441 -0.00636 -2.61503
 N 4.16568 -1.38332 -1.51463
 C 3.76392 -0.07675 -1.61292
 C 3.20145 -2.35581 -1.01096
 H 2.82132 -2.98327 -1.82405
 H 3.69037 -3.00479 -0.27416
 O 0.40998 -2.52922 -1.83004
 O -0.21312 1.49010 -0.98785
 C 0.65375 3.34276 0.22314
 C -0.50319 4.08479 -0.06614
 C 1.56565 3.87123 1.15166
 C -0.73577 5.31940 0.53736
 H -1.20373 3.66262 -0.77921
 C 1.32936 5.10167 1.76563
 H 2.46082 3.31572 1.41208

C 0.17990 5.83347 1.45880
 H -1.63140 5.88353 0.28915
 H 2.04462 5.48971 2.48622
 H -0.00011 6.79388 1.93424
 C -1.68031 0.15500 1.24516
 C -1.54266 -1.22312 -0.60972
 H -2.23614 -0.03773 2.16614
 H -1.55644 1.22447 1.06894
 N -0.35177 -1.37538 -0.03853
 N -2.36916 -0.44160 0.09284
 S -2.20028 -1.81191 -2.09452
 C 2.35295 0.22369 -1.26123
 C 2.06771 -1.55226 -0.39800
 H 2.19431 -1.30642 0.65142
 H 1.62916 0.07017 -2.06451
 C -0.05240 -1.45728 2.44818
 C 0.77737 -0.97832 3.46912
 C -0.66935 -2.70613 2.59993
 C 0.98225 -1.73045 4.62714
 H 1.26839 -0.01528 3.35375
 C -0.46009 -3.46014 3.75423
 H -1.30083 -3.09892 1.80773
 C 0.36393 -2.97296 4.77169
 H 1.63125 -1.34891 5.40978
 H -0.93727 -4.43029 3.85764
 H 0.52774 -3.56256 5.66884
 C -0.29557 -0.58626 1.23035
 H 0.50125 0.15042 1.12744
 C -4.65147 0.57688 -0.03463
 C -5.80805 0.65324 -0.81053
 C -5.91532 -0.04085 -2.02258
 C -4.86212 -0.82821 -2.49347
 C -3.70336 -0.90798 -1.72645
 C -3.60375 -0.21195 -0.50728
 H -4.56423 1.11775 0.90163
 H -6.63675 1.26407 -0.46713
 H -6.82603 0.03554 -2.60765
 H -4.94370 -1.35873 -3.43693

SCF = -1521.19632754
 H(0 K) = -1520.705726
 H(298 K) = -1520.676074
 G(298 K) = -1520.769816
 SCF (BS2) = -1521.56191770
 SCF (DCM) = -1521.21549970
 Lowest Frequency = -319.1932cm⁻¹

62
 46trans
 C 2.03118 1.46033 -0.40469
 C 0.73232 1.94902 -0.46554
 C 0.81299 -1.69215 -0.95540
 H 2.82521 2.00737 0.09003
 C 5.66442 -1.20955 -1.79076
 H 6.20070 -2.14717 -1.79316
 C 4.96218 0.95377 -1.89014
 H 4.94311 2.02574 -2.02504
 C 6.08048 0.08150 -2.06275
 H 7.08546 0.37092 -2.33992
 N 4.33473 -1.13576 -1.45228
 C 3.89508 0.16126 -1.51774

| | | | |
|---|----------|----------|----------|
| C | 3.29871 | -2.10500 | -1.14359 |
| H | 2.96110 | -2.63253 | -2.04251 |
| H | 3.64966 | -2.84475 | -0.41579 |
| O | 0.53584 | -2.29549 | -1.98192 |
| O | -0.23461 | 1.33879 | -1.05298 |
| C | 0.39198 | 3.25255 | 0.22921 |
| C | -0.80492 | 3.89291 | -0.13190 |
| C | 1.18231 | 3.84819 | 1.22715 |
| C | -1.19108 | 5.09316 | 0.46483 |
| H | -1.41047 | 3.41743 | -0.89680 |
| C | 0.79468 | 5.04408 | 1.83150 |
| H | 2.10099 | 3.36549 | 1.54627 |
| C | -0.39291 | 5.67565 | 1.45185 |
| H | -2.11558 | 5.57724 | 0.15846 |
| H | 1.41988 | 5.48359 | 2.60495 |
| H | -0.69207 | 6.60850 | 1.92242 |
| C | -1.64502 | 0.09831 | 1.24164 |
| C | -1.50649 | -1.25864 | -0.62903 |
| H | -2.15523 | -0.11515 | 2.18418 |
| H | -1.58562 | 1.16983 | 1.04566 |
| N | -0.27544 | -1.33395 | -0.11046 |
| N | -2.34663 | -0.54753 | 0.12124 |
| S | -2.18190 | -1.85375 | -2.09954 |
| C | 2.42608 | 0.27651 | -1.21947 |
| C | 2.17146 | -1.21462 | -0.57290 |
| H | 2.27553 | -1.11927 | 0.50869 |
| H | 1.84104 | 0.27942 | -2.15139 |
| C | 0.09804 | -1.45286 | 2.36232 |
| C | 1.00891 | -0.99140 | 3.32046 |
| C | -0.51269 | -2.70112 | 2.54718 |
| C | 1.29936 | -1.75957 | 4.44970 |
| H | 1.49387 | -0.02940 | 3.17620 |
| C | -0.21879 | -3.47058 | 3.67220 |
| H | -1.21033 | -3.08073 | 1.80507 |
| C | 0.68615 | -3.00007 | 4.62735 |
| H | 2.00955 | -1.39108 | 5.18390 |
| H | -0.69357 | -4.43870 | 3.80256 |
| H | 0.91513 | -3.60134 | 5.50222 |
| C | -0.22678 | -0.56456 | 1.17786 |
| H | 0.52841 | 0.21749 | 1.06791 |
| C | -4.69006 | 0.33031 | 0.10352 |
| C | -5.87802 | 0.34837 | -0.62535 |
| C | -5.99086 | -0.32910 | -1.84745 |
| C | -4.91230 | -1.03934 | -2.37705 |
| C | -3.72112 | -1.05964 | -1.65594 |
| C | -3.61566 | -0.38336 | -0.42656 |
| H | -4.59794 | 0.85891 | 1.04615 |
| H | -6.72849 | 0.90015 | -0.23834 |
| H | -6.92766 | -0.29871 | -2.39416 |
| H | -4.99842 | -1.55501 | -3.32811 |

SCF = -1521.20060953
 H(0 K) = -1520.708644
 H(298 K) = -1520.678899
 G(298 K) = -1520.772280
 SCF (BS2) = -1521.56705130
 SCF (DCM) = -1521.22277090
 Lowest Frequency = 16.6390cm⁻¹

62
 TS2trans

| | | | |
|---|----------|----------|----------|
| C | 2.36726 | 1.67892 | -0.61839 |
| C | 1.03859 | 2.03037 | -0.56249 |
| C | 0.68337 | -1.14668 | -1.18576 |
| H | 3.15866 | 2.26041 | -0.16194 |
| C | 5.63528 | -1.67227 | -1.39175 |
| H | 5.96018 | -2.69931 | -1.31232 |
| C | 5.42069 | 0.58583 | -1.59471 |
| H | 5.65024 | 1.63335 | -1.72958 |
| C | 6.34728 | -0.50272 | -1.58780 |
| H | 7.42142 | -0.43385 | -1.69751 |
| N | 4.31349 | -1.31721 | -1.26814 |
| C | 4.16771 | 0.04164 | -1.39942 |
| C | 3.05581 | -2.03557 | -1.14620 |
| H | 2.74581 | -2.46826 | -2.10451 |
| H | 3.12242 | -2.83650 | -0.40215 |
| O | 0.38637 | -1.55624 | -2.29801 |
| O | 0.11564 | 1.28673 | -1.09556 |
| C | 0.57879 | 3.26487 | 0.16853 |
| C | -0.73108 | 3.72149 | -0.05663 |
| C | 1.37551 | 3.97437 | 1.08373 |
| C | -1.22464 | 4.85101 | 0.59743 |
| H | -1.33722 | 3.17077 | -0.76878 |
| C | 0.88348 | 5.10195 | 1.73995 |
| H | 2.38430 | 3.63363 | 1.29545 |
| C | -0.41984 | 5.54782 | 1.50106 |
| H | -2.23743 | 5.19297 | 0.39676 |
| H | 1.51763 | 5.63244 | 2.44599 |
| H | -0.80101 | 6.42686 | 2.01381 |
| C | -1.78828 | 0.08675 | 1.33543 |
| C | -1.64452 | -1.04839 | -0.67171 |
| H | -2.22002 | -0.22447 | 2.28870 |
| H | -1.81421 | 1.17483 | 1.23396 |
| N | -0.39099 | -1.07784 | -0.22527 |
| N | -2.50900 | -0.52299 | 0.20848 |
| S | -2.34851 | -1.50640 | -2.18016 |
| C | 2.71661 | 0.42714 | -1.35157 |
| C | 2.08549 | -0.90407 | -0.71488 |
| H | 2.12892 | -0.79566 | 0.36966 |
| H | 2.30286 | 0.46882 | -2.37292 |
| C | 0.09116 | -1.46095 | 2.20419 |
| C | 1.00819 | -1.05666 | 3.18182 |
| C | -0.43650 | -2.75844 | 2.25896 |
| C | 1.38653 | -1.93018 | 4.20326 |
| H | 1.43188 | -0.05654 | 3.13743 |
| C | -0.05535 | -3.63238 | 3.27648 |
| H | -1.13586 | -3.09362 | 1.49766 |
| C | 0.85495 | -3.21915 | 4.25264 |
| H | 2.10193 | -1.60494 | 4.95261 |
| H | -0.46600 | -4.63744 | 3.30572 |
| H | 1.15243 | -3.90189 | 5.04300 |
| C | -0.33570 | -0.46746 | 1.14096 |
| H | 0.35793 | 0.37018 | 1.09646 |
| C | -4.92943 | 0.07942 | 0.42408 |
| C | -6.15879 | 0.05304 | -0.23430 |
| C | -6.27887 | -0.47769 | -1.52521 |
| C | -5.16667 | -0.99156 | -2.19594 |
| C | -3.93530 | -0.96718 | -1.54707 |
| C | -3.82221 | -0.43841 | -0.24714 |
| H | -4.83378 | 0.49220 | 1.42275 |
| H | -7.03561 | 0.45256 | 0.26493 |
| H | -7.24711 | -0.48753 | -2.01495 |

H -5.25988 -1.39341 -3.19989
 SCF = -1521.19957720
 H(0 K)= -1520.707826
 H(298 K)= -1520.678926
 G(298 K)= -1520.769906
 SCF (BS2) = -1521.56565989
 SCF (DCM) = -1521.22222157
 Lowest Frequency = -23.0392cm⁻¹

32

21trans

C 0.08104 -0.81725 -0.32921
 C 1.10092 0.05674 -0.25303
 C -0.36009 2.01993 -0.19182
 H 0.25177 -1.88130 -0.22863
 C -4.67877 -0.51082 0.51087
 H -5.50879 0.07992 0.86917
 C -3.24158 -2.13330 -0.19302
 H -2.83841 -3.09326 -0.48350
 C -4.57414 -1.86484 0.24769
 H -5.36609 -2.59050 0.37288
 N -3.44981 0.04471 0.25981
 C -2.57016 -0.93004 -0.17071
 C -2.88620 1.39678 0.27254
 H -3.16919 1.96395 -0.62290
 H -3.20235 1.95817 1.15494
 O -0.49471 3.19930 -0.38623
 O 0.87823 1.43758 -0.39007
 C 2.53206 -0.24749 -0.06302
 C 3.42796 0.75769 0.33794
 C 3.02751 -1.54699 -0.27167
 C 4.77552 0.46409 0.54339
 H 3.06205 1.76711 0.48433
 C 4.37263 -1.83602 -0.06197
 H 2.36303 -2.33183 -0.61844
 C 5.25357 -0.83201 0.34895
 H 5.45297 1.25359 0.85557
 H 4.73684 -2.84522 -0.23100
 H 6.30404 -1.05802 0.50678
 C -1.28888 -0.25340 -0.56382
 C -1.39325 1.04113 0.28024
 H -1.11396 0.75738 1.30502
 H -1.36023 0.02686 -1.63259

SCF = -822.703471174
 H(0 K)= -822.448741
 H(298 K)= -822.434475
 G(298 K)= -822.491180
 SCF (BS2) = -822.914217548
 SCF (DCM) = -822.712193029
 Lowest Frequency = 26.9661cm⁻¹

(c)21trans formation from (E)-45

62

(E)-45

C -1.79394 2.61065 0.05195
 C -2.41741 1.34215 0.42295
 C 2.05305 0.29393 -1.72917
 H -2.40234 3.50372 -0.02883

C 2.20680 4.94128 -0.96942
 H 3.26899 5.09938 -1.09309
 C -0.02504 5.11604 -0.82275
 H -1.03785 5.49495 -0.83077
 C 1.14606 5.83615 -1.09518
 H 1.22820 6.88201 -1.35513
 N 1.72670 3.71558 -0.63945
 C 0.33718 3.78815 -0.54289
 C 2.59144 2.51042 -0.44398
 H 3.59323 2.93282 -0.29662
 H 2.31548 2.07042 0.51406
 O 1.99380 -0.42286 -2.76197
 O -1.76052 0.29200 0.53157
 C -3.89885 1.29561 0.67876
 C -4.50541 0.03161 0.76549
 C -4.69614 2.43833 0.85104
 C -5.87147 -0.08836 1.00235
 H -3.87667 -0.84325 0.64043
 C -6.06383 2.31851 1.09838
 H -4.25529 3.42844 0.81339
 C -6.65598 1.05652 1.16976
 H -6.32770 -1.07285 1.05733
 H -6.66660 3.21159 1.23626
 H -7.72231 0.96527 1.35671
 C 0.57604 -1.42696 1.46301
 C 0.71374 -1.51898 -0.83758
 H 1.03402 -2.08471 2.20549
 H -0.32653 -0.95494 1.85666
 N 1.42120 -0.43458 -0.55697
 N 0.24171 -2.16134 0.24421
 S 0.28772 -2.25145 -2.34592
 C -0.45586 2.65626 -0.19746
 C 2.57835 1.55137 -1.58225
 H 3.00500 1.92625 -2.50776
 H 0.05628 1.70324 -0.13138
 C 3.02679 -0.60539 1.36727
 C 3.42517 -0.15696 2.63378
 C 3.94025 -1.30773 0.57263
 C 4.71049 -0.41964 3.10769
 H 2.72723 0.40370 3.25221
 C 5.22752 -1.56602 1.04674
 H 3.65582 -1.63383 -0.42276
 C 5.61496 -1.12784 2.31405
 H 5.00664 -0.06454 4.09053
 H 5.93023 -2.10563 0.41869
 H 6.61825 -1.32904 2.67804
 C 1.59410 -0.35634 0.92369
 H 1.26395 0.62058 1.27837
 C -1.26635 -4.05485 0.87794
 C -2.04620 -5.09436 0.36737
 C -2.14765 -5.31137 -1.01181
 C -1.47147 -4.48818 -1.91716
 C -0.69734 -3.44419 -1.42002
 C -0.59629 -3.23830 -0.03139
 H -1.18660 -3.88420 1.94652
 H -2.58119 -5.74247 1.05443
 H -2.75983 -6.12616 -1.38525
 H -1.55352 -4.65720 -2.98671

SCF = -1521.20776626
 H(0 K)= -1520.717444

H(298 K)= -1520.686680
 G(298 K)= -1520.784418
 SCF (BS2) = -1521.57418896
 SCF (DCM) = -1521.22656178
 Lowest Frequency = 6.2476cm⁻¹

62

TS1trans(E)

| | | | |
|---|----------|----------|----------|
| C | 0.48206 | 2.85157 | -0.02894 |
| C | 1.48589 | 1.92948 | -0.42882 |
| C | -0.97100 | 0.31060 | 1.65116 |
| H | 0.73562 | 3.79144 | 0.44636 |
| C | -4.20635 | 3.81719 | 0.00503 |
| H | -5.21964 | 3.62353 | 0.32642 |
| C | -2.24663 | 4.66603 | -0.76344 |
| H | -1.51025 | 5.31020 | -1.22250 |
| C | -3.64145 | 4.92103 | -0.60781 |
| H | -4.17034 | 5.81885 | -0.89791 |
| N | -3.20012 | 2.90700 | 0.21585 |
| C | -2.00373 | 3.40797 | -0.24296 |
| C | -3.16029 | 1.60484 | 0.88087 |
| H | -3.88363 | 1.60154 | 1.70576 |
| H | -3.45740 | 0.80232 | 0.19453 |
| O | -0.18095 | 0.18723 | 2.59654 |
| O | 1.22677 | 0.75324 | -0.82542 |
| C | 2.93575 | 2.34273 | -0.37971 |
| C | 3.91331 | 1.34187 | -0.49098 |
| C | 3.35867 | 3.67535 | -0.25198 |
| C | 5.27037 | 1.65646 | -0.45649 |
| H | 3.57287 | 0.31900 | -0.61131 |
| C | 4.71634 | 3.99374 | -0.22180 |
| H | 2.62481 | 4.47265 | -0.19701 |
| C | 5.67828 | 2.98568 | -0.31941 |
| H | 6.01275 | 0.86646 | -0.54011 |
| H | 5.02432 | 5.03182 | -0.12791 |
| H | 6.73575 | 3.23516 | -0.29512 |
| C | -0.48413 | -1.71698 | -1.47792 |
| C | 0.23030 | -1.52176 | 0.69640 |
| H | -0.90135 | -2.53437 | -2.06785 |
| H | 0.06499 | -1.00211 | -2.09763 |
| N | -0.87626 | -0.77547 | 0.67858 |
| N | 0.42435 | -2.21040 | -0.43655 |
| S | 1.48616 | -1.68790 | 1.86354 |
| C | -0.86754 | 2.46521 | -0.16486 |
| C | -1.72908 | 1.49151 | 1.37458 |
| H | -1.54827 | 2.18633 | 2.19273 |
| H | -0.95075 | 1.63802 | -0.87011 |
| C | -2.85960 | -1.79712 | -0.47290 |
| C | -3.82977 | -1.69157 | -1.47974 |
| C | -3.08710 | -2.66371 | 0.60187 |
| C | -5.00087 | -2.44611 | -1.41915 |
| H | -3.67083 | -1.01030 | -2.31271 |
| C | -4.26166 | -3.41638 | 0.66395 |
| H | -2.35619 | -2.74005 | 1.40072 |
| C | -5.21898 | -3.31260 | -0.34590 |
| H | -5.74537 | -2.34983 | -2.20387 |
| H | -4.42825 | -4.08139 | 1.50625 |
| H | -6.13286 | -3.89680 | -0.29372 |
| C | -1.57490 | -0.99561 | -0.61960 |
| H | -1.79172 | -0.03044 | -1.07251 |
| C | 2.12613 | -3.67789 | -1.54029 |

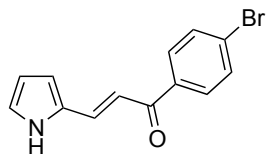
| | | | |
|---|---------|----------|----------|
| C | 3.35473 | -4.31200 | -1.35698 |
| C | 4.06118 | -4.18868 | -0.15326 |
| C | 3.55826 | -3.41869 | 0.89746 |
| C | 2.33441 | -2.77801 | 0.72105 |
| C | 1.62771 | -2.91195 | -0.48754 |
| H | 1.57811 | -3.77161 | -2.47186 |
| H | 3.76803 | -4.91004 | -2.16277 |
| H | 5.01444 | -4.69371 | -0.03520 |
| H | 4.11248 | -3.31503 | 1.82508 |

SCF = -1521.17910204
 H(0 K)= -1520.688842
 H(298 K)= -1520.659264
 G(298 K)= -1520.752283
 SCF (BS2) = -1521.54548644
 SCF (DCM) = -1521.19981767
 Lowest Frequency = -319.2877cm⁻¹

1.7 References and Notes

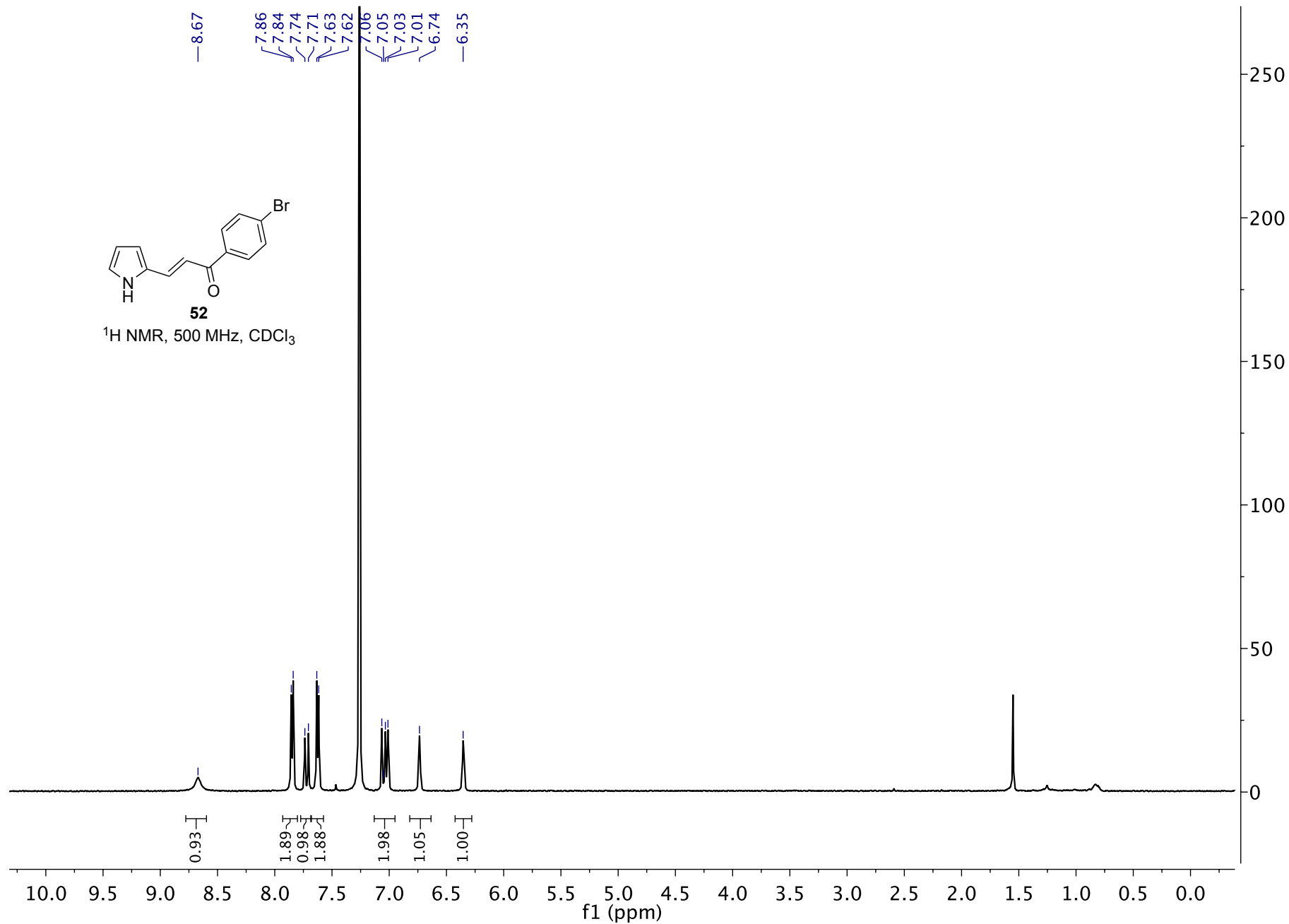
- [1] K. R. Law, C. S. P. McErlean, *Chem. Eur. J.* **2013**, *19*, 15852-15855.
- [2] B. A. Trofimov, A. b. I. Mikhaleva, A. V. Ivanov, V. S. Shcherbakova, I. A. Ushakov, *Tetrahedron* **2015**, *71*, 124-128.
- [3] L. Sun, N. Tran, C. Liang, S. Hubbard, F. Tang, K. Lipson, R. Schreck, Y. Zhou, G. McMahon, C. Tang, *J. Med. Chem.* **2000**, *43*, 2655-2663.
- [4] T. P. Robinson, R. B. Hubbard Iv, T. J. Ehlers, J. L. Arbiser, D. J. Goldsmith, J. P. Bowen, *Biorg. Med. Chem.* **2005**, *13*, 4007-4013.
- [5] N. R. El-Rayyes, *J. Heterocycl. Chem.* **1982**, *19*, 415-419.
- [6] W. Herz, J. A. Y. Brasch, *J. Org. Chem.* **1958**, *23*, 1513-1516.
- [7] I. A. Ushakov, A. V. Afonin, V. K. Voronov, Z. V. Stepanova, L. N. Sobenina, A. I. Mikhaleva, *Russ. J. Org. Chem.* **2003**, *39*, 1318-1324.
- [8] Gaussian 09, Revision D.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2009.
- [9] Y. Zhao and D. G. Truhlar, *Theor. Chem. Acc.*, 2008, *120* 215
- [10] (i) W. J. Hehre, R. Ditchfield and J. A. Pople, *J. Chem. Phys.* **1972**, *56*, 2257. (ii) P. C. Hariharan and J. A. Pople, *Theor. Chim. Acta.* **1973**, *28*, 213.
- [11] (i) A. D. McLean and G. S. Chandler, *J. Chem. Phys.*, **1980** *72*, 5639 (ii) K. Raghavachari, J. S. Binkley, R. Seeger, and J. A. Pople, *J. Chem. Phys.*, **1980**, *72*, 650; (iii) T. Clark, J. Chandrasekhar, G. W. Spitznagel, and P. v. R. Schleyer, *J. Comp. Chem.*, **1983**, *4*, 294
- [12] J. Tomasi, B. Mennucci, and R. Cammi, *Chem. Rev.*, **2005**, *105*, 2999
- [13] A. D. Becke, *J. Chem. Phys.*, **1993**, *98*, 5648

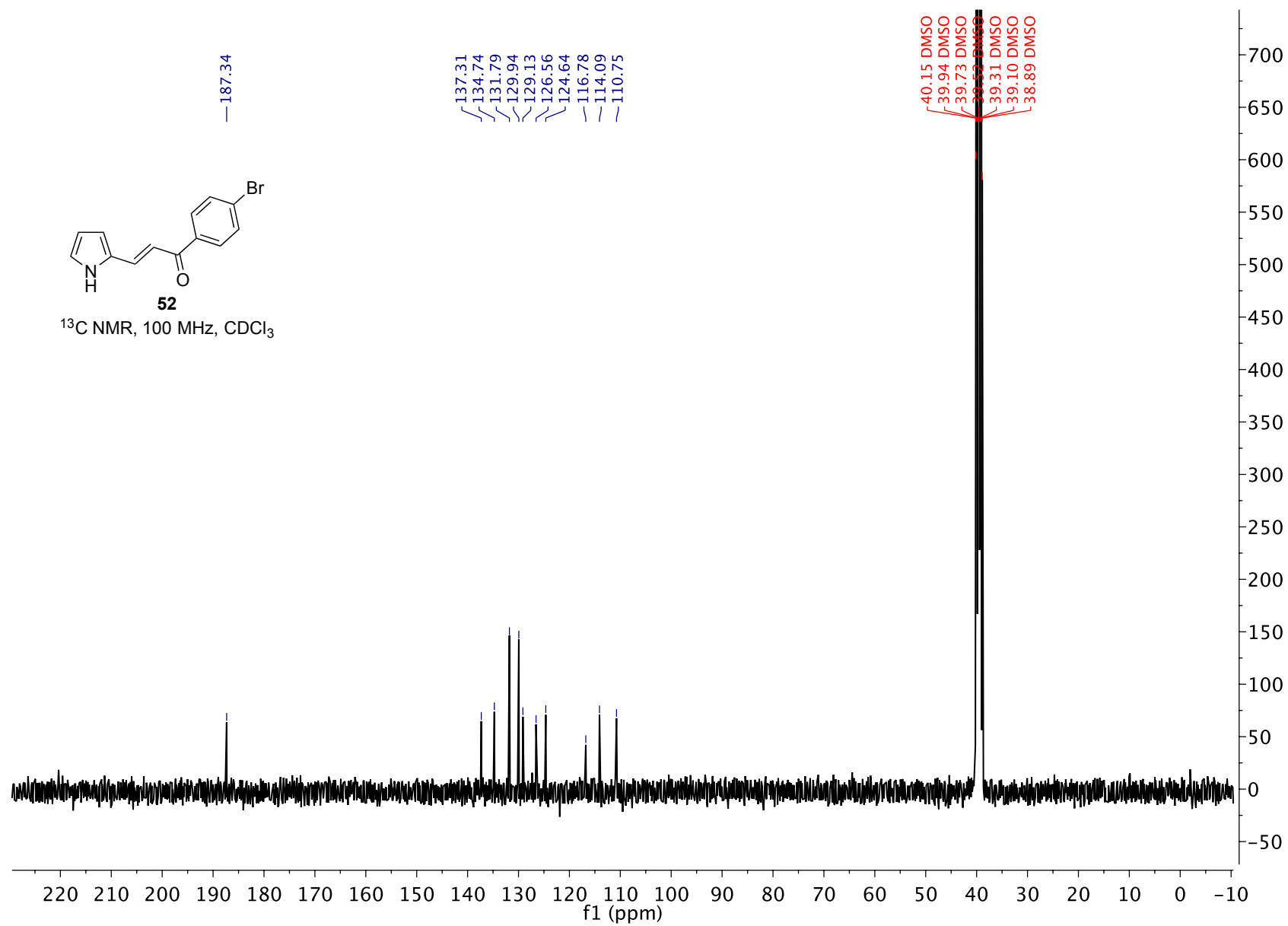
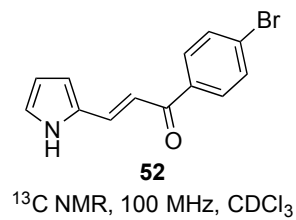
1.8 ¹H NMR, ¹³C{¹H} NMR and HPLC Data for Novel Compounds

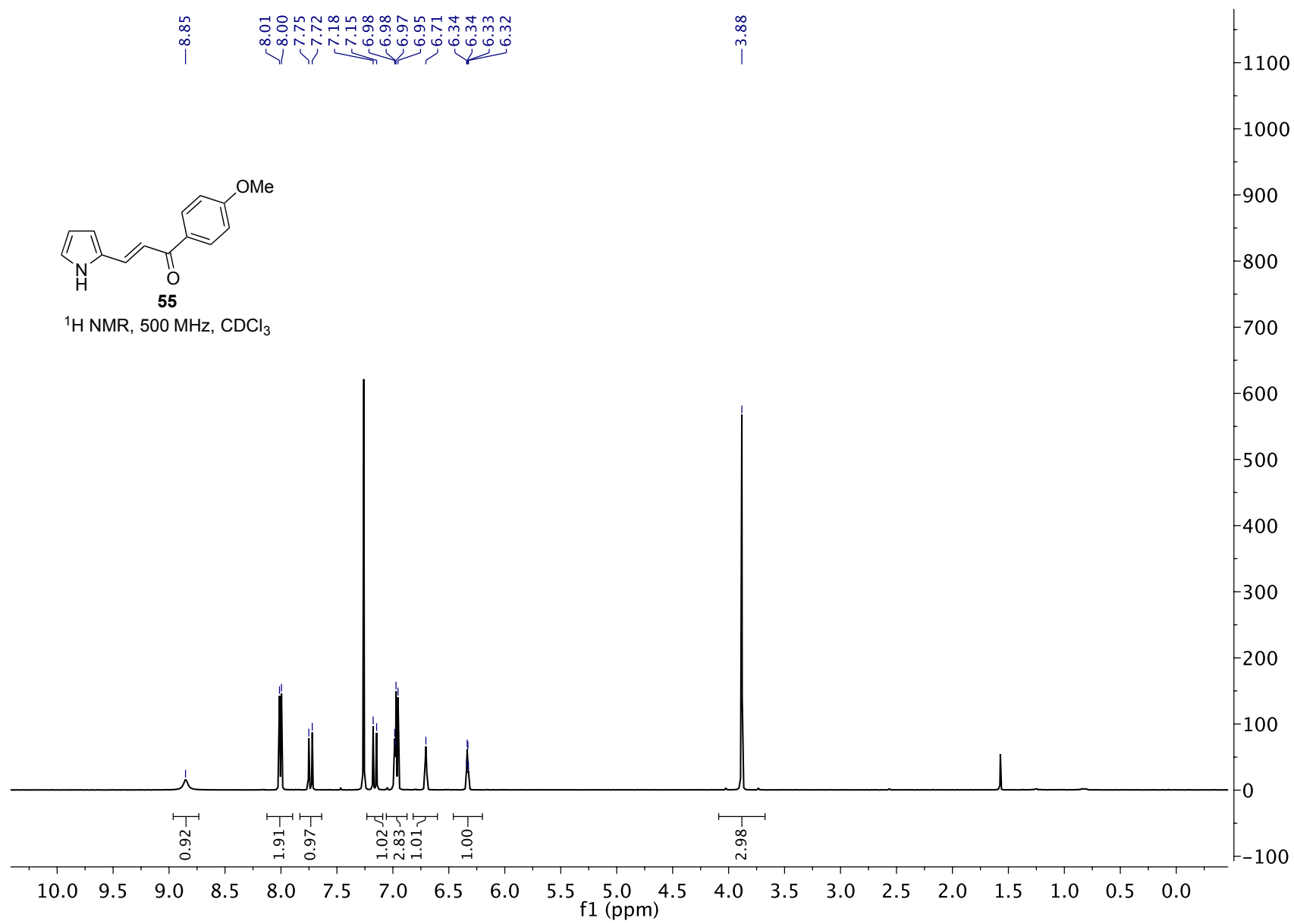


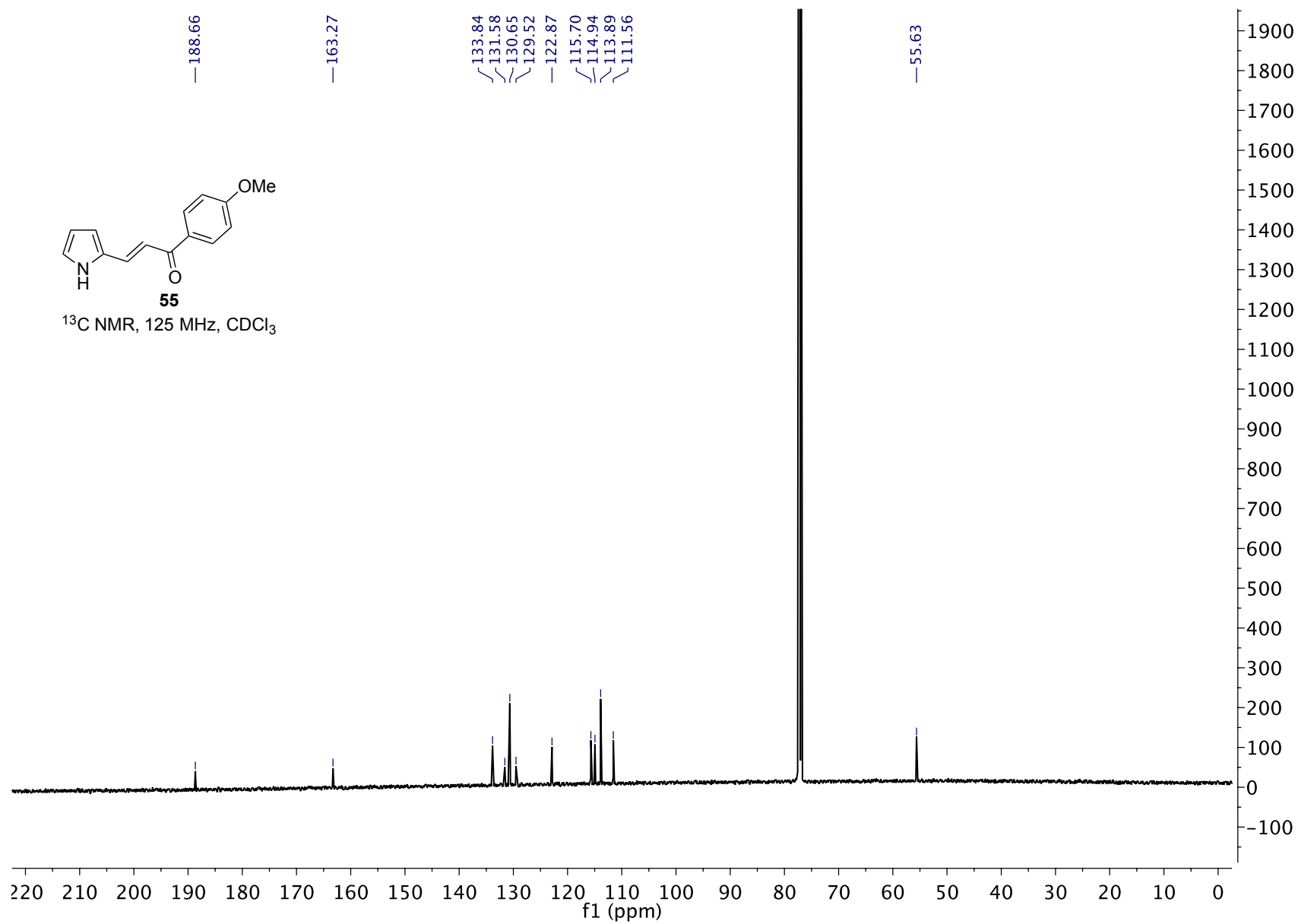
52

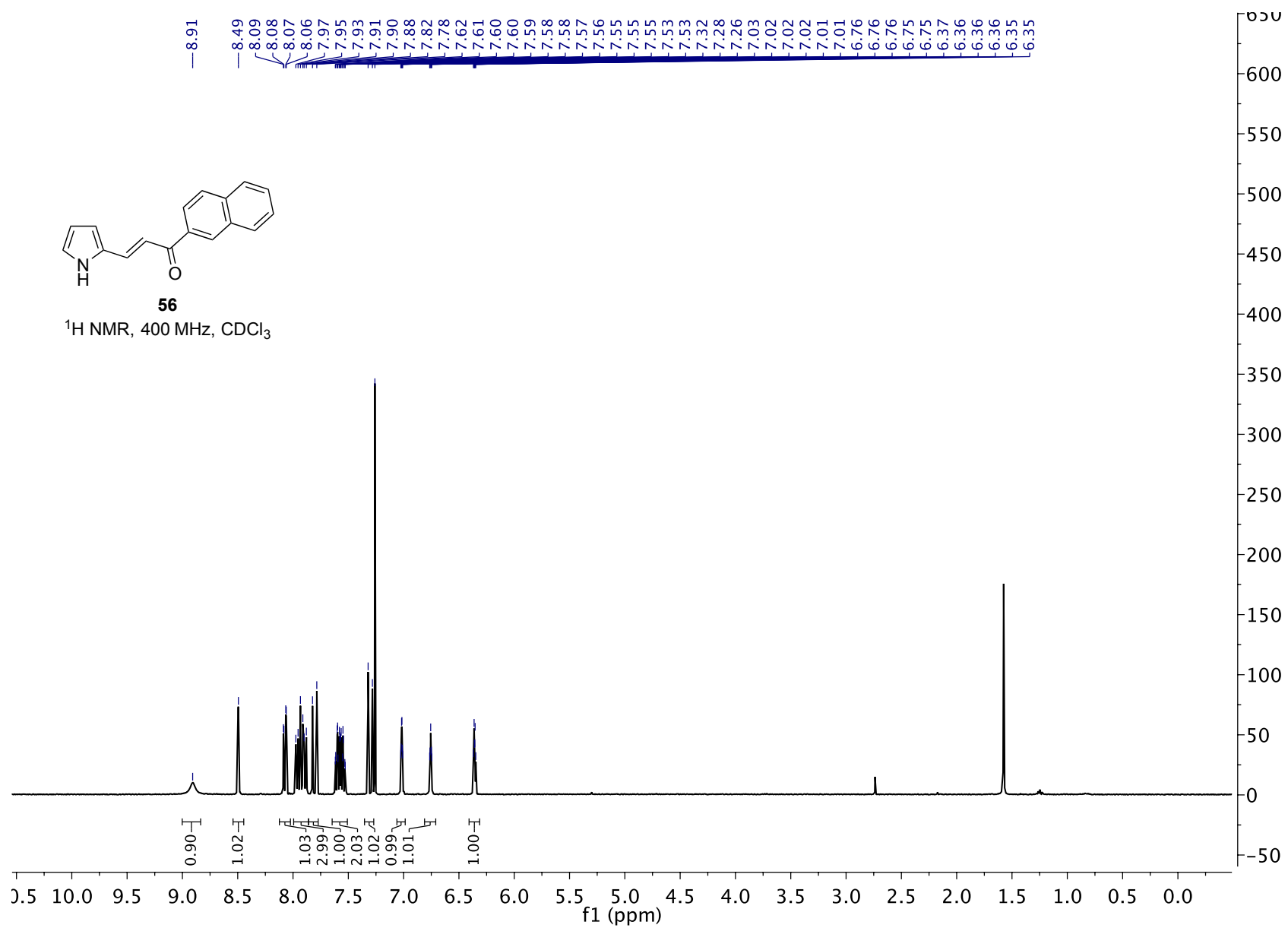
¹H NMR, 500 MHz, CDCl₃

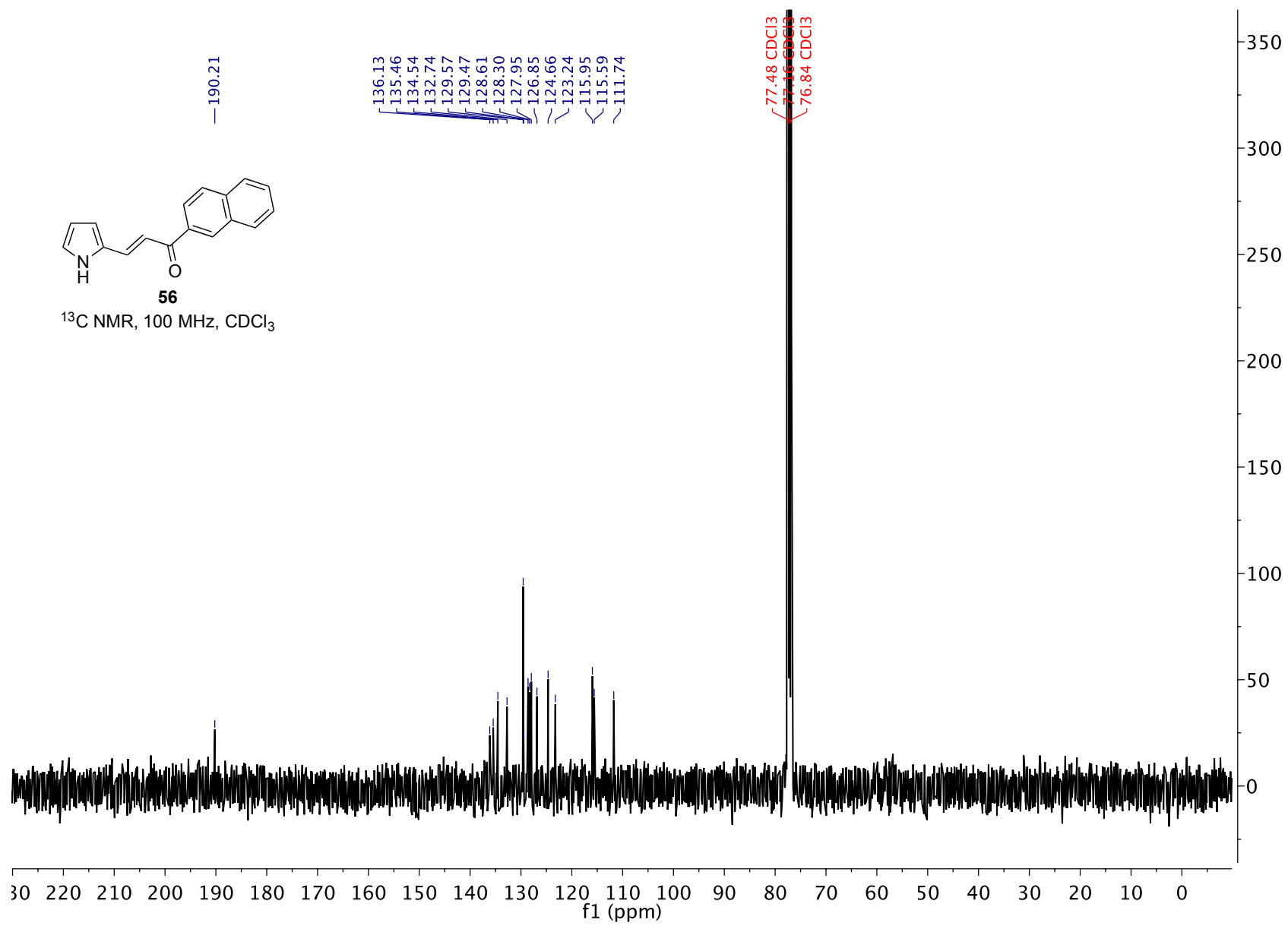


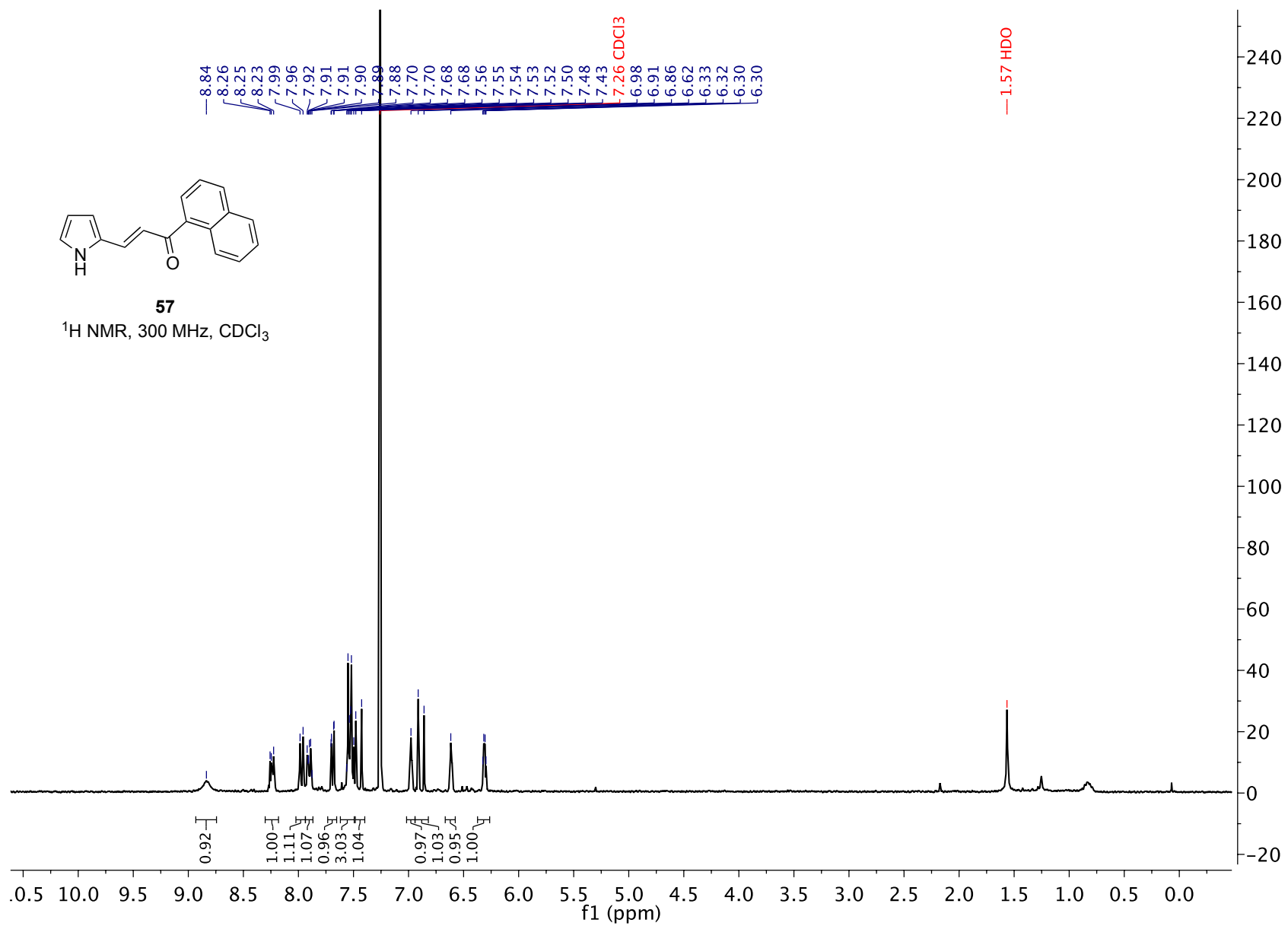


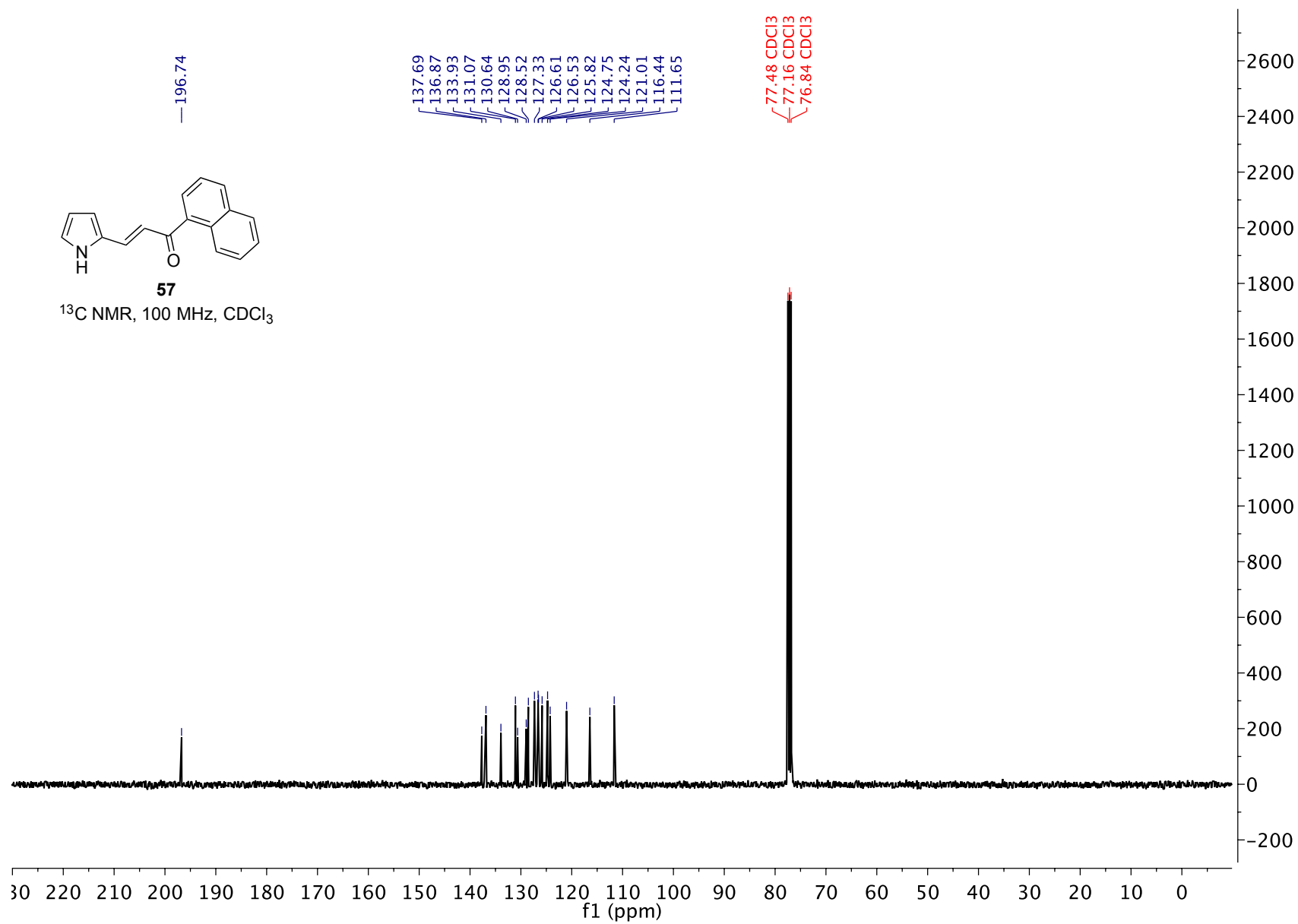


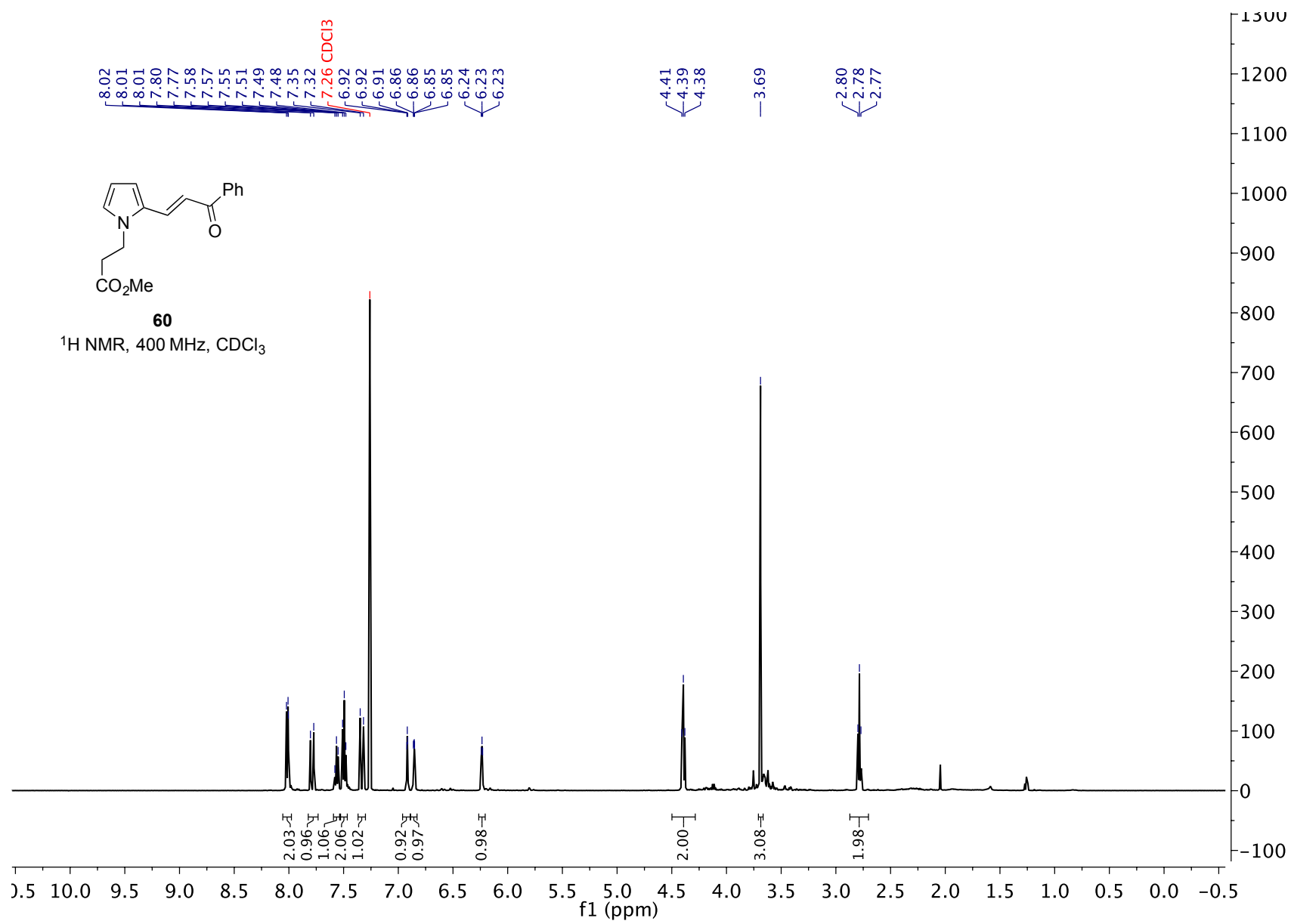


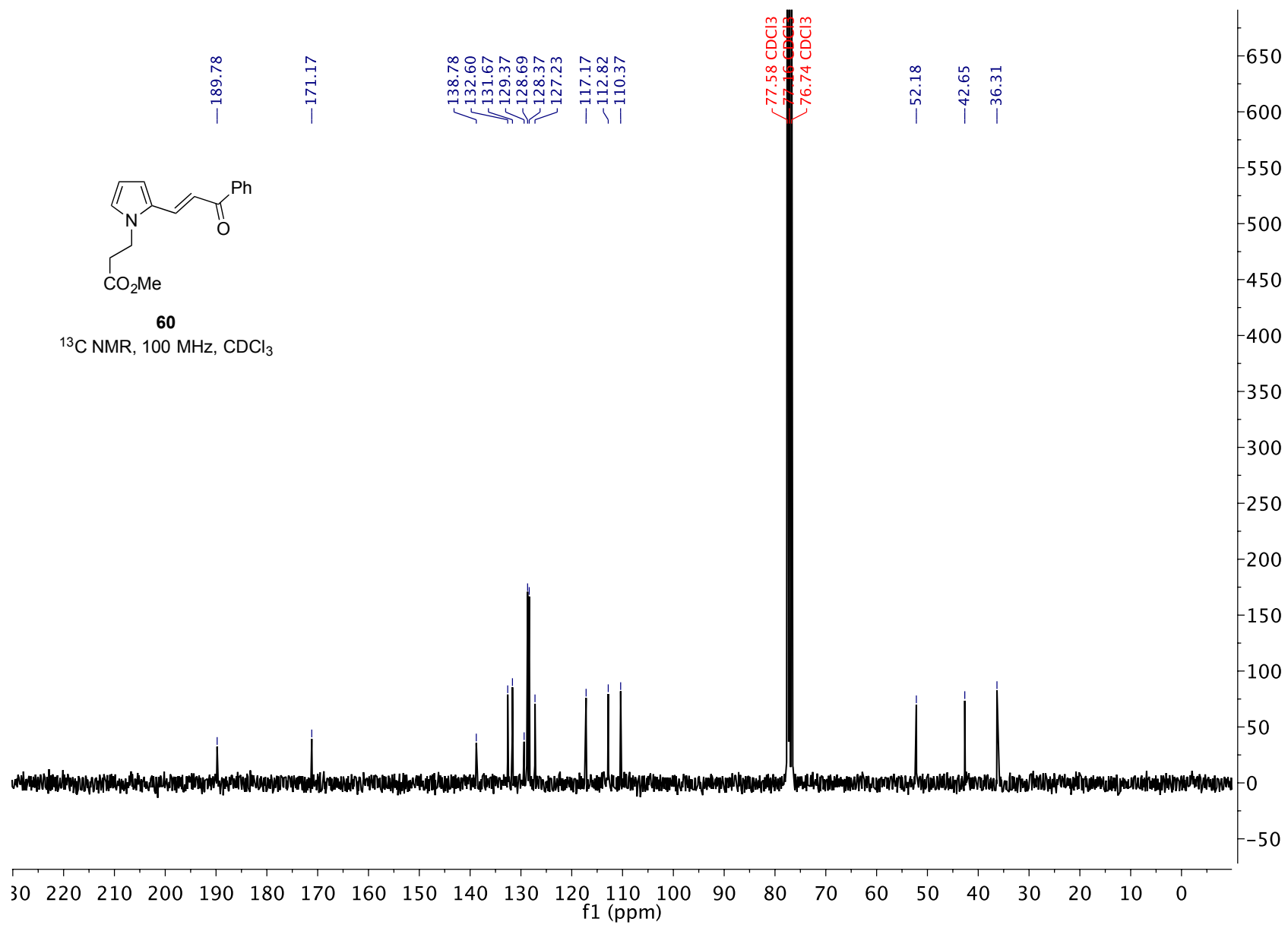


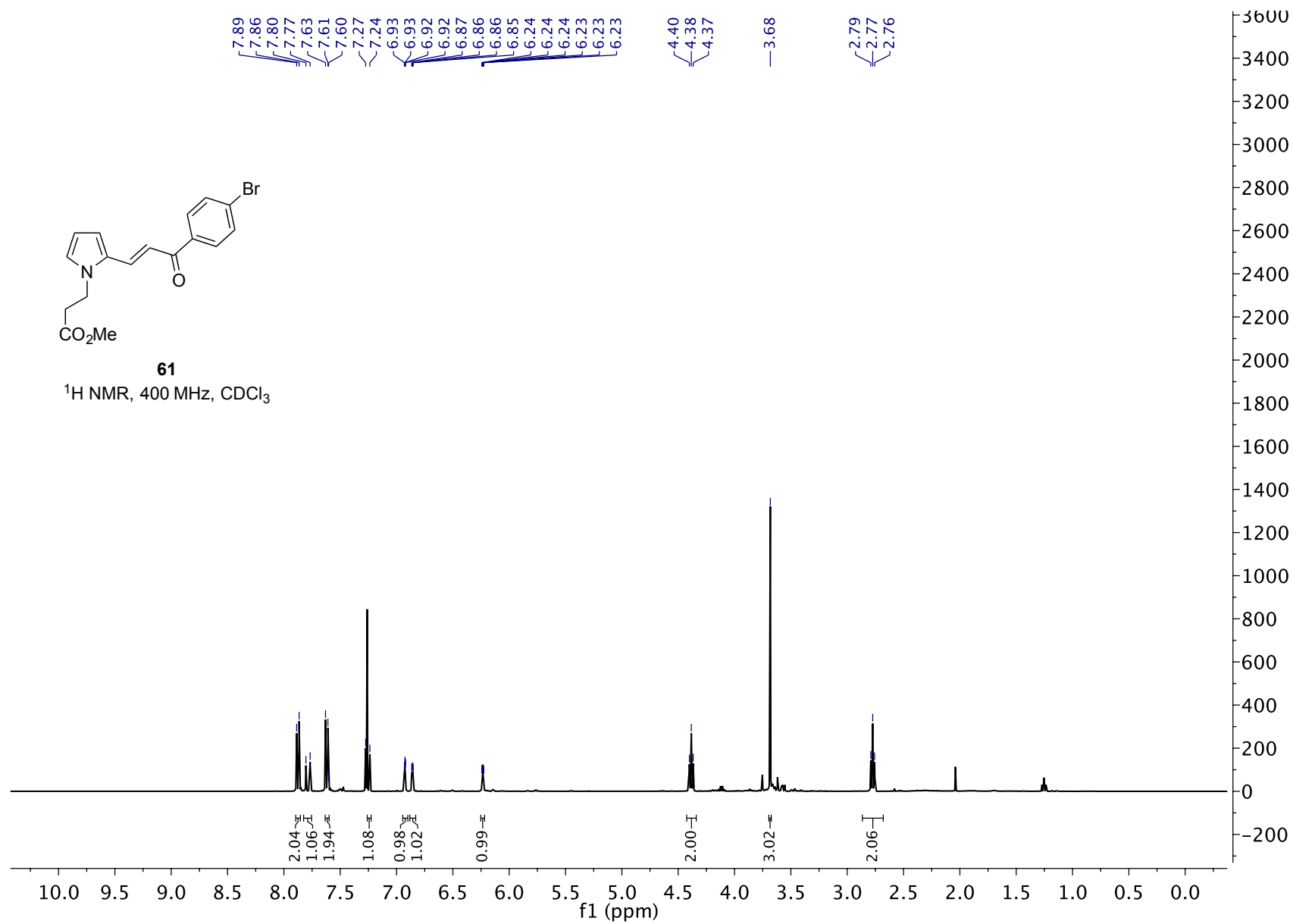


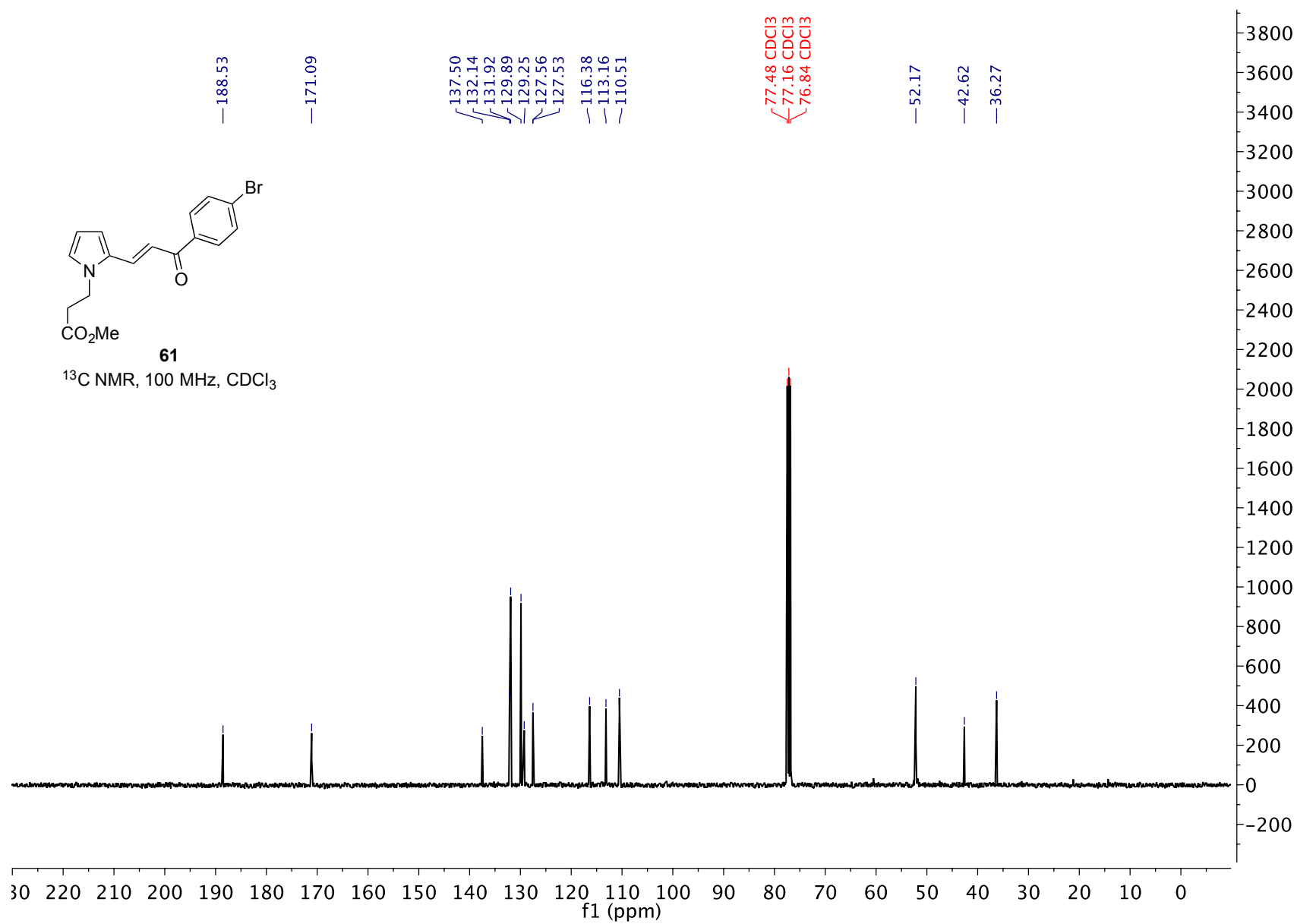


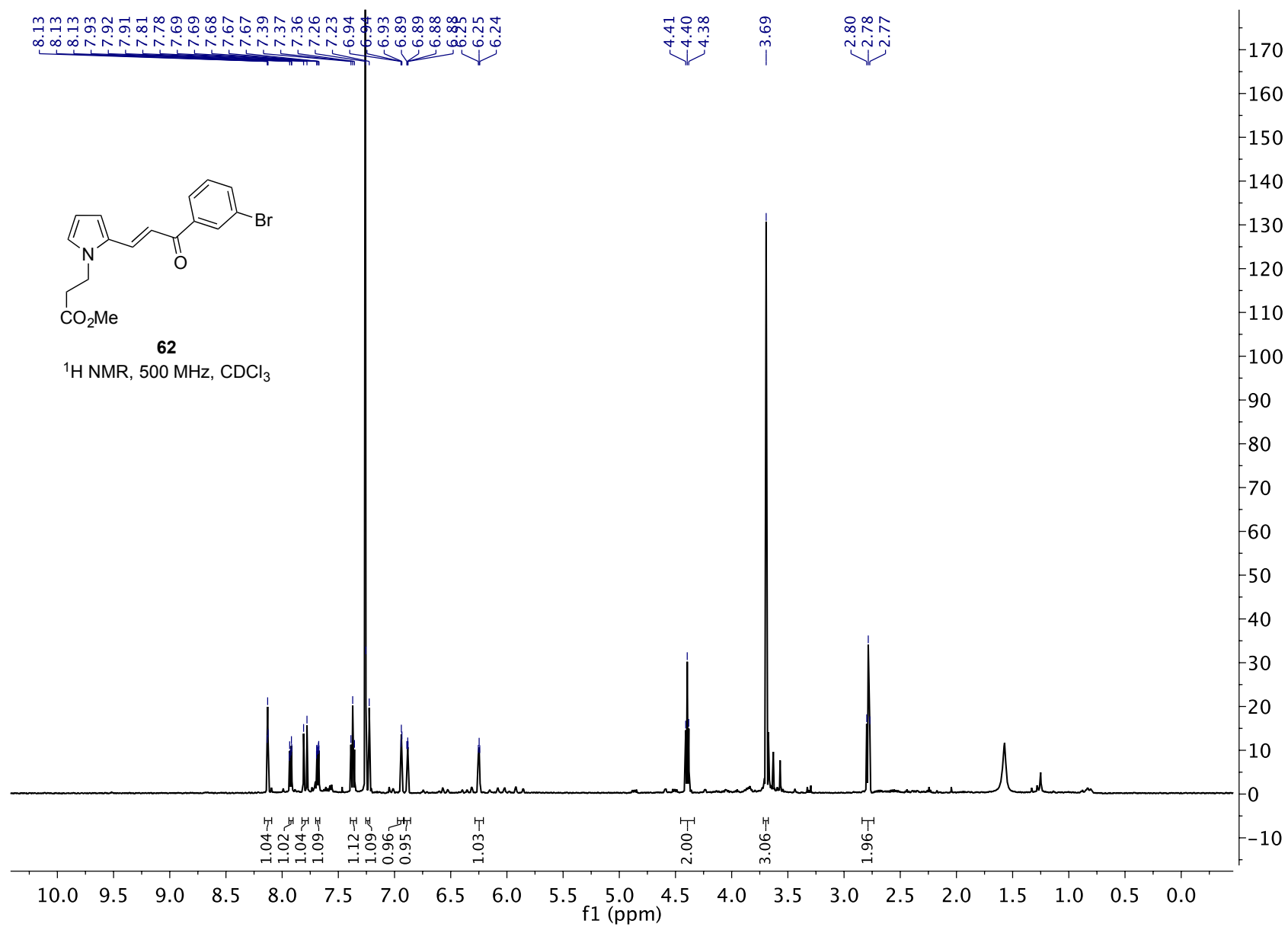


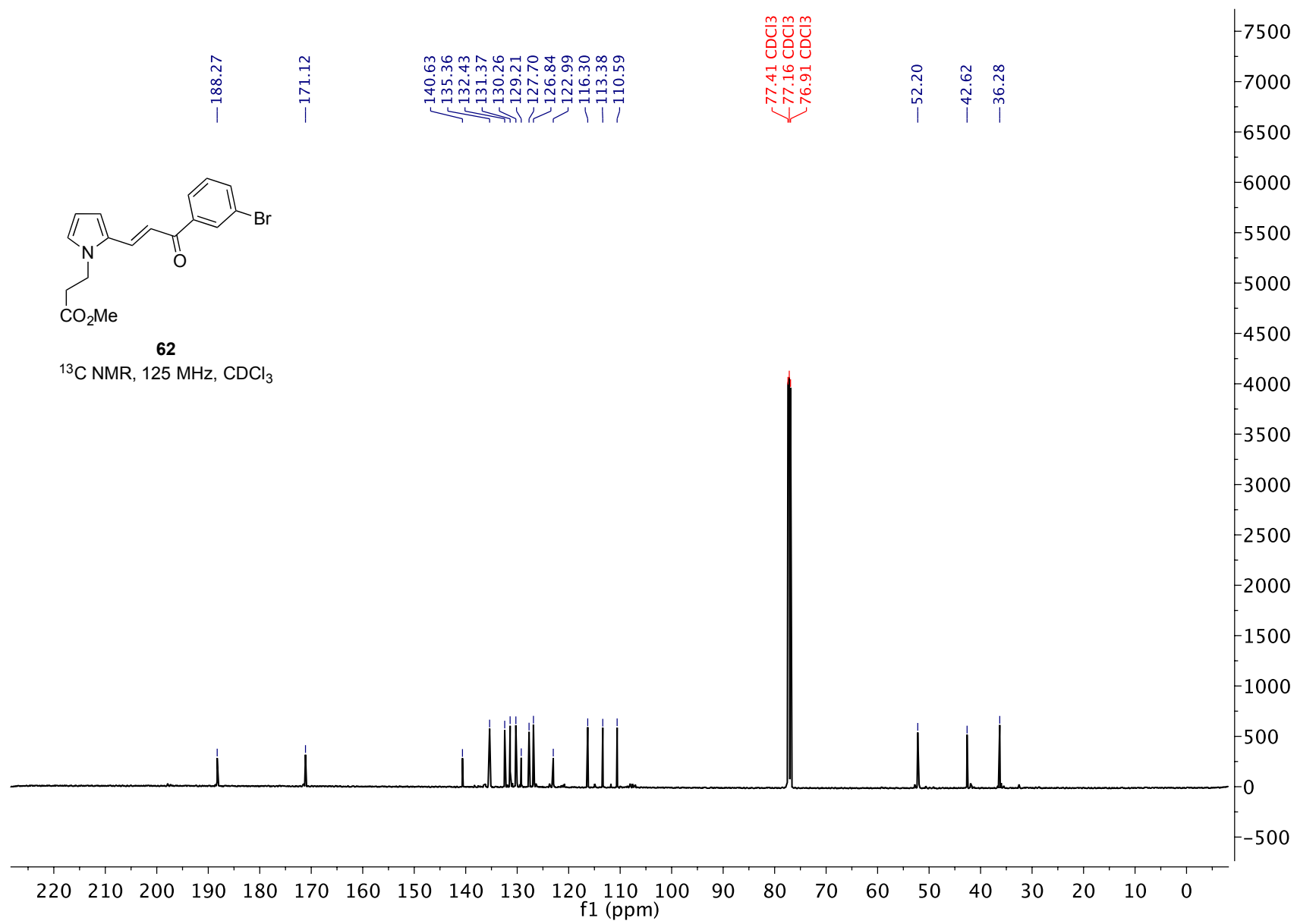


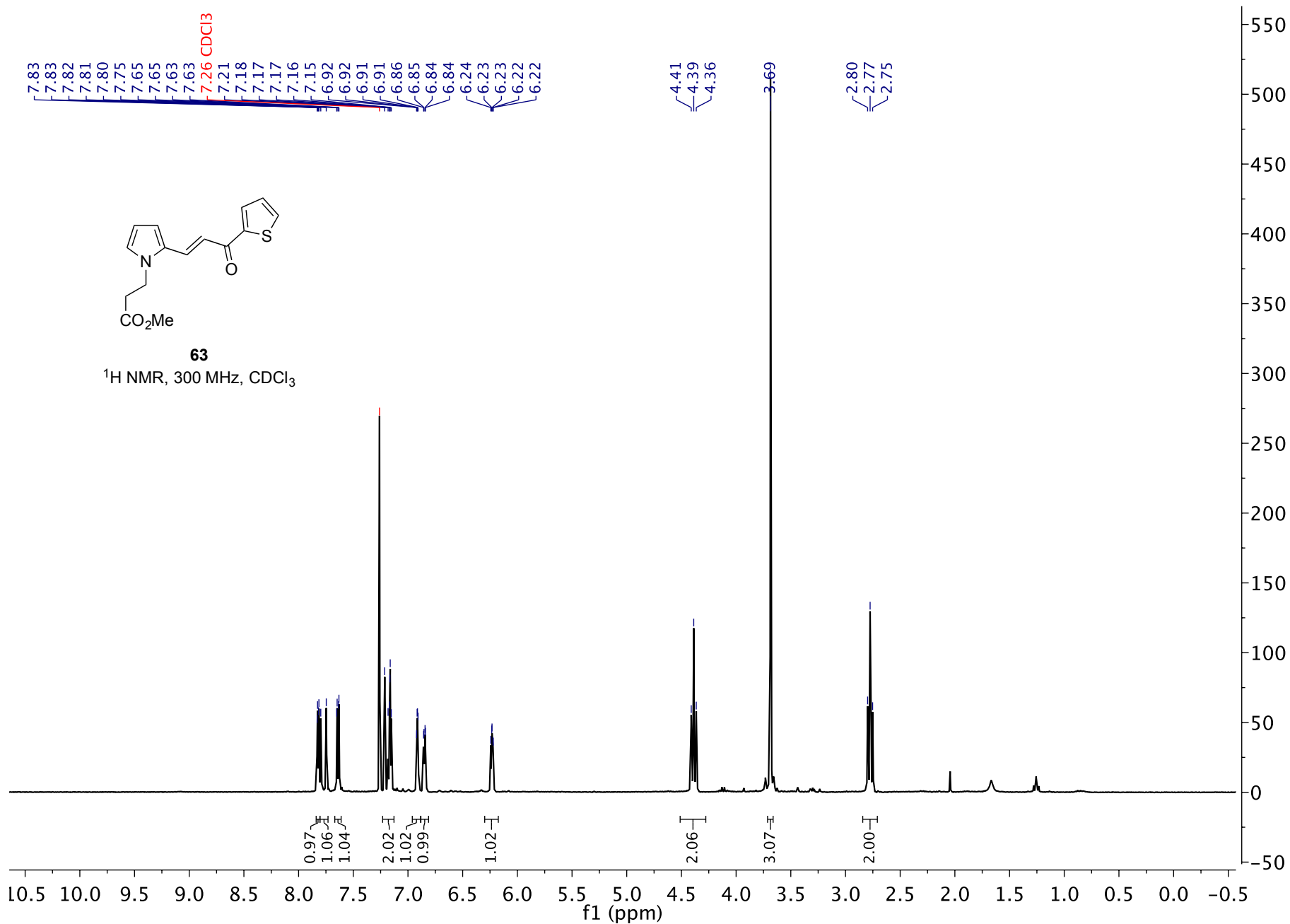


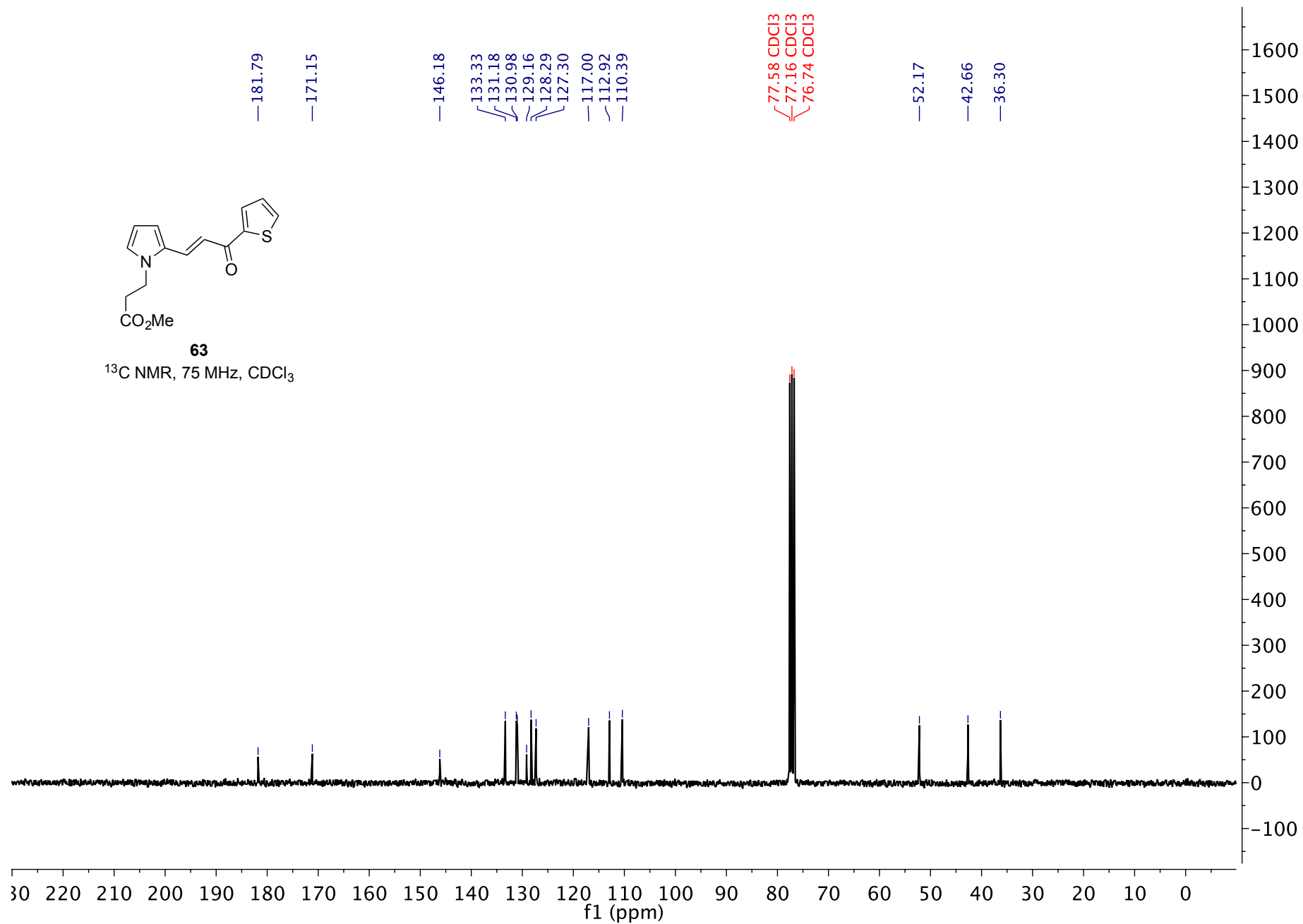
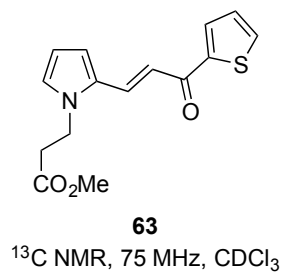


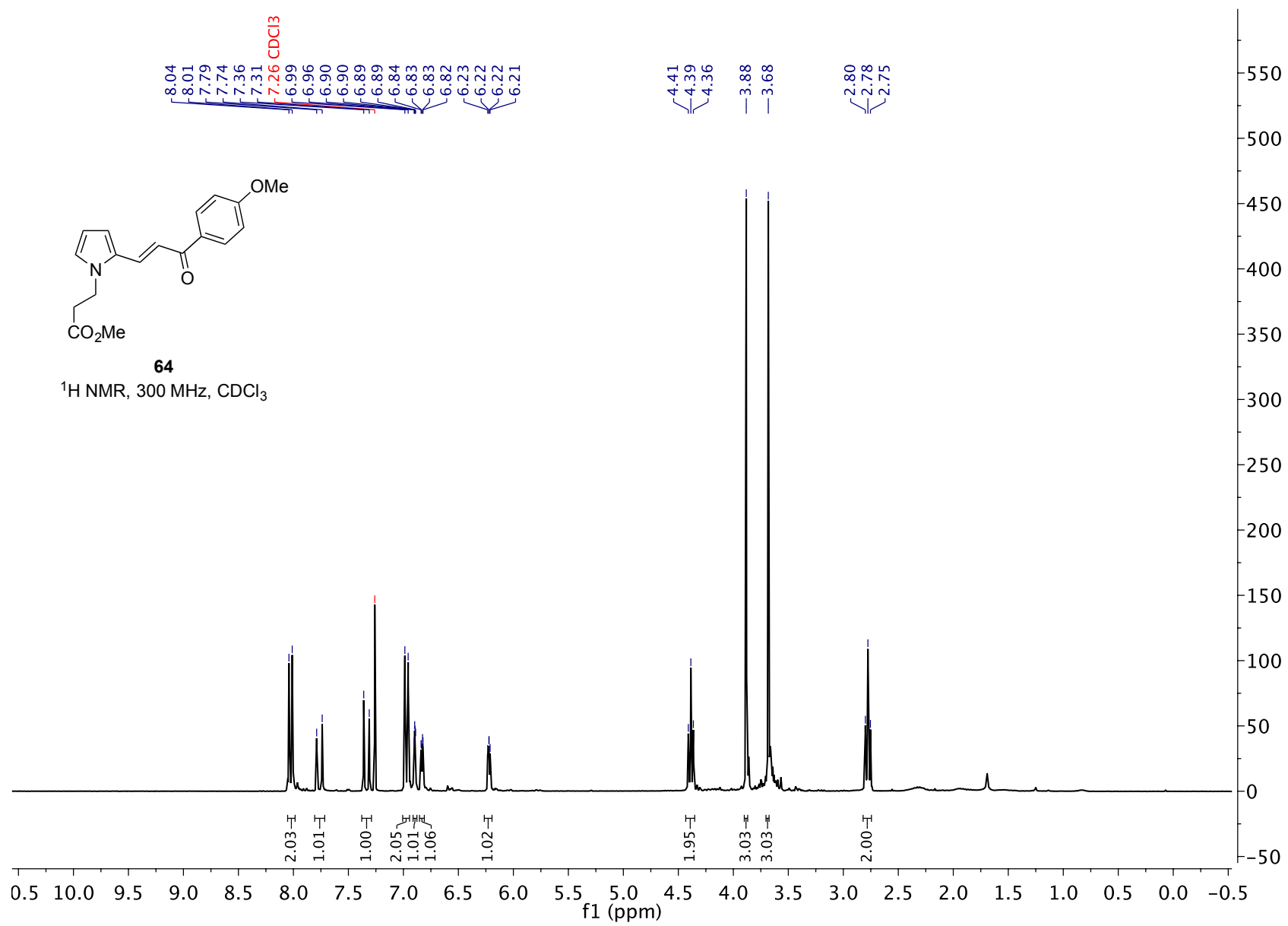


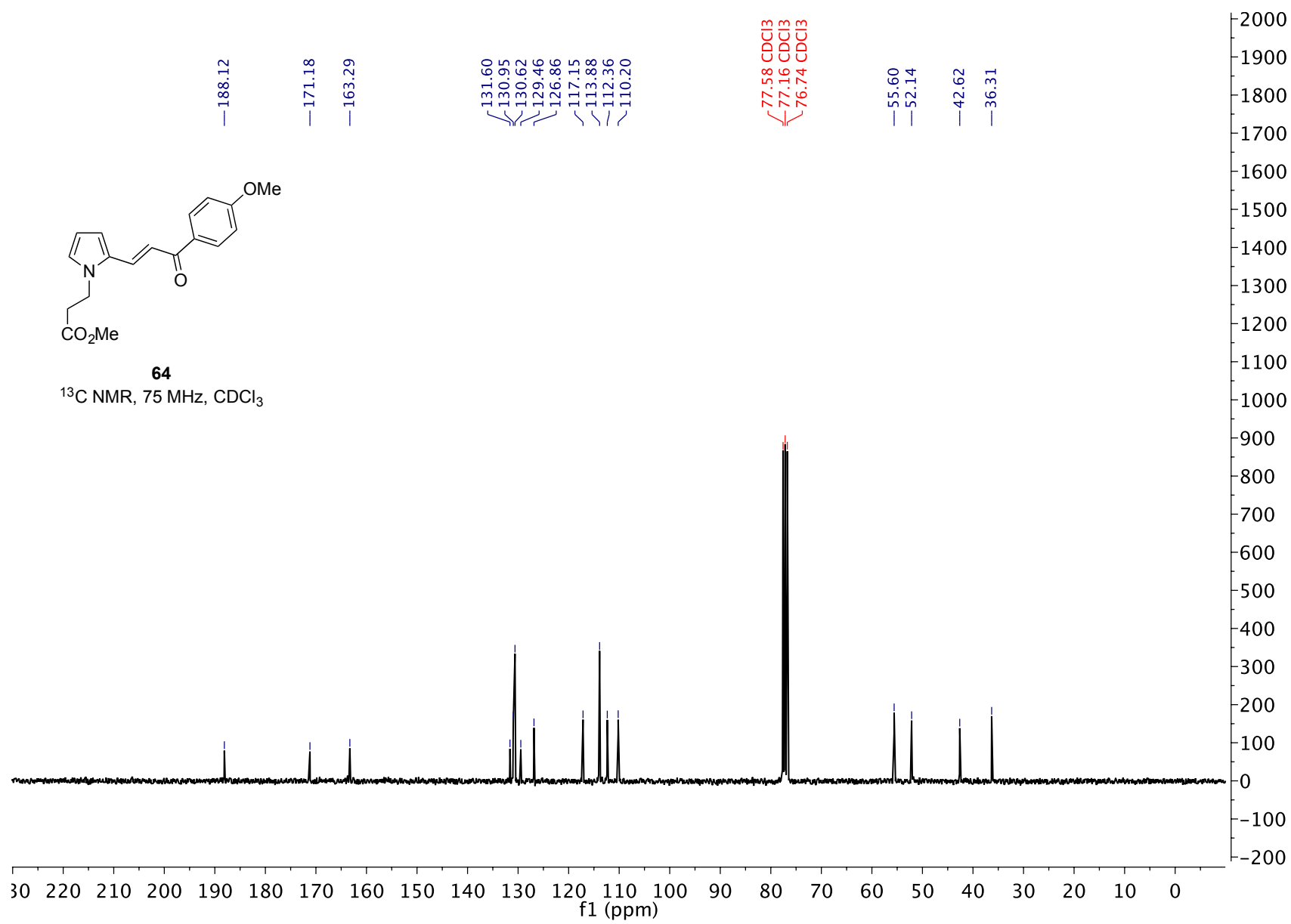


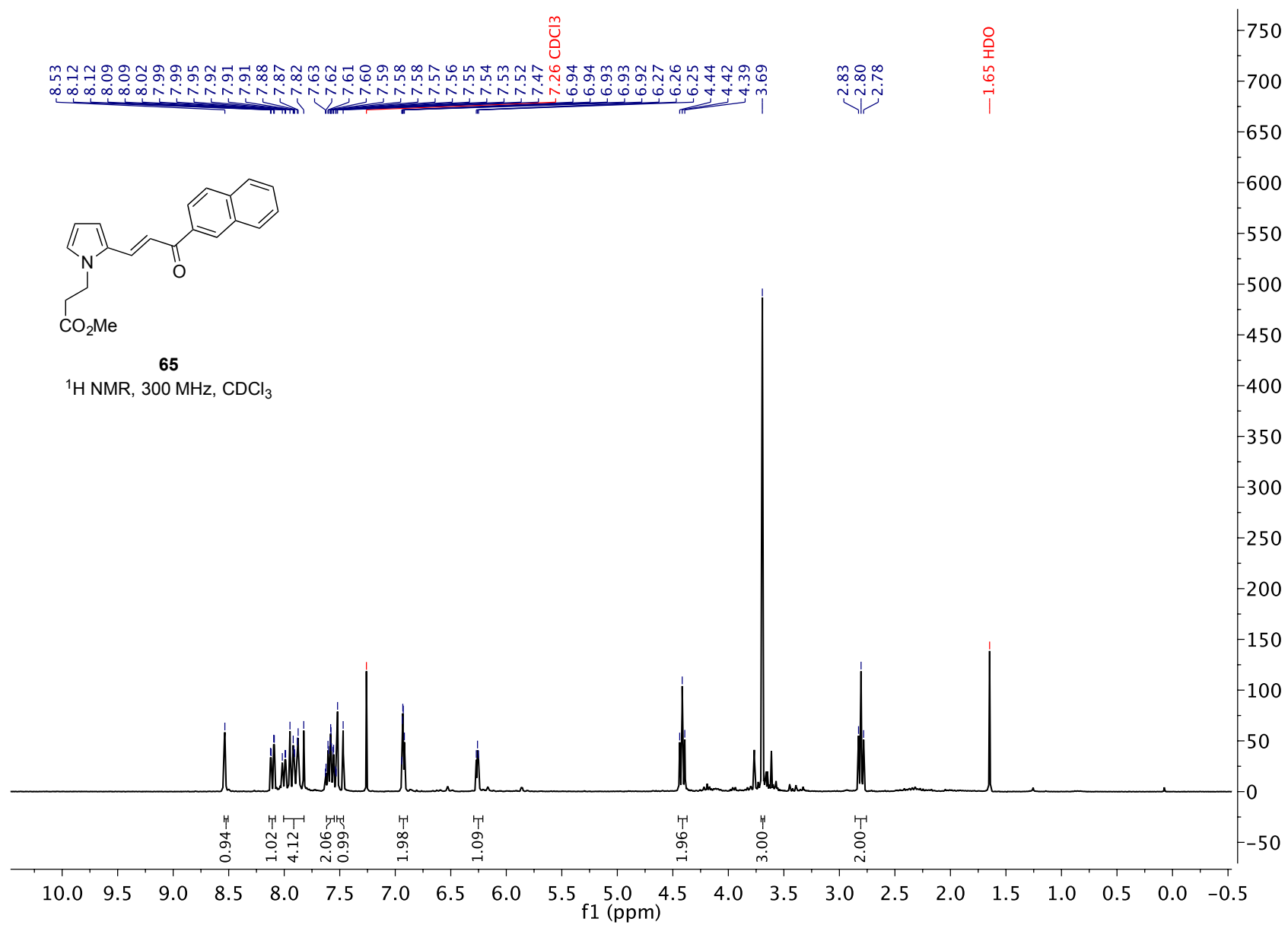


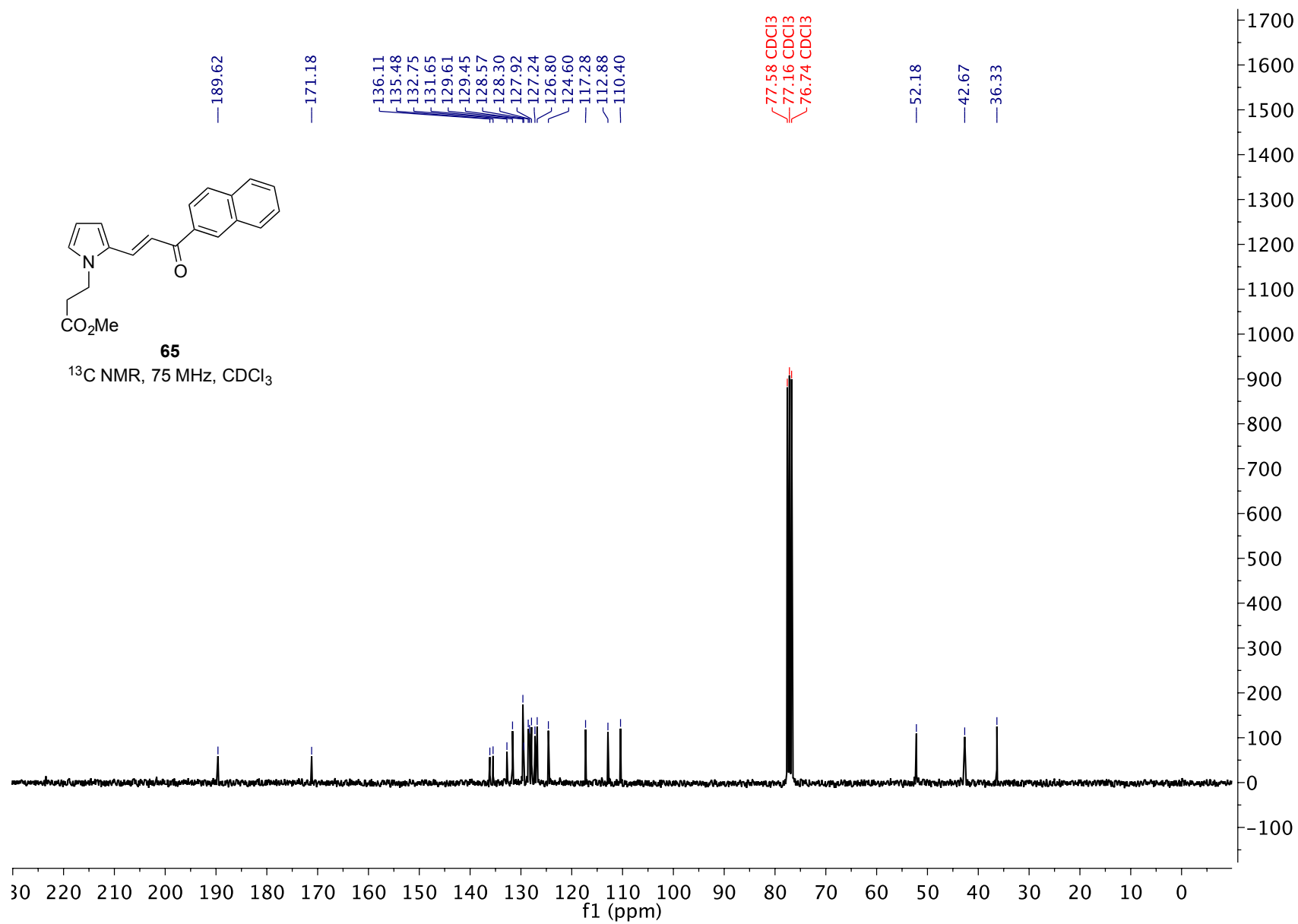


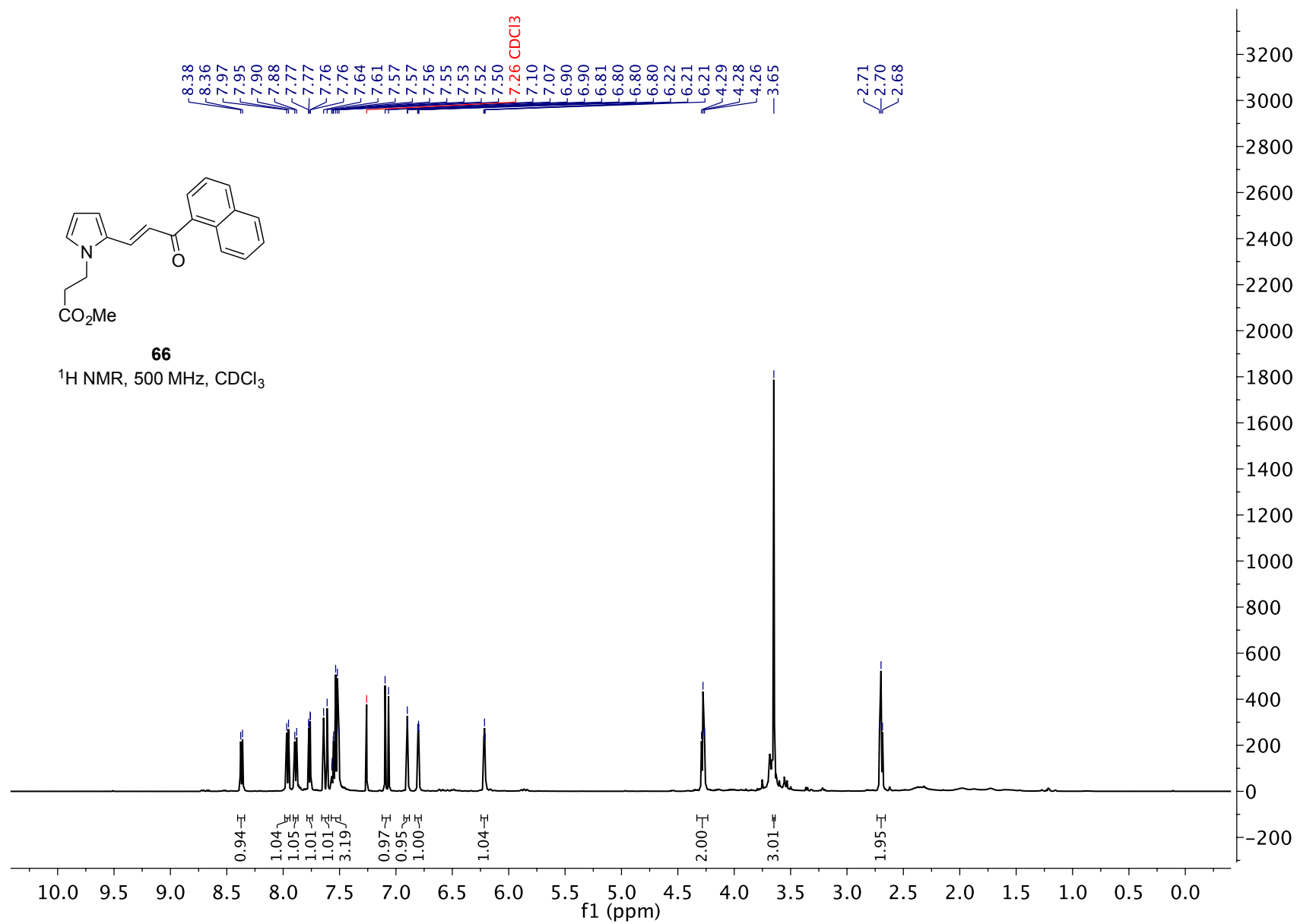


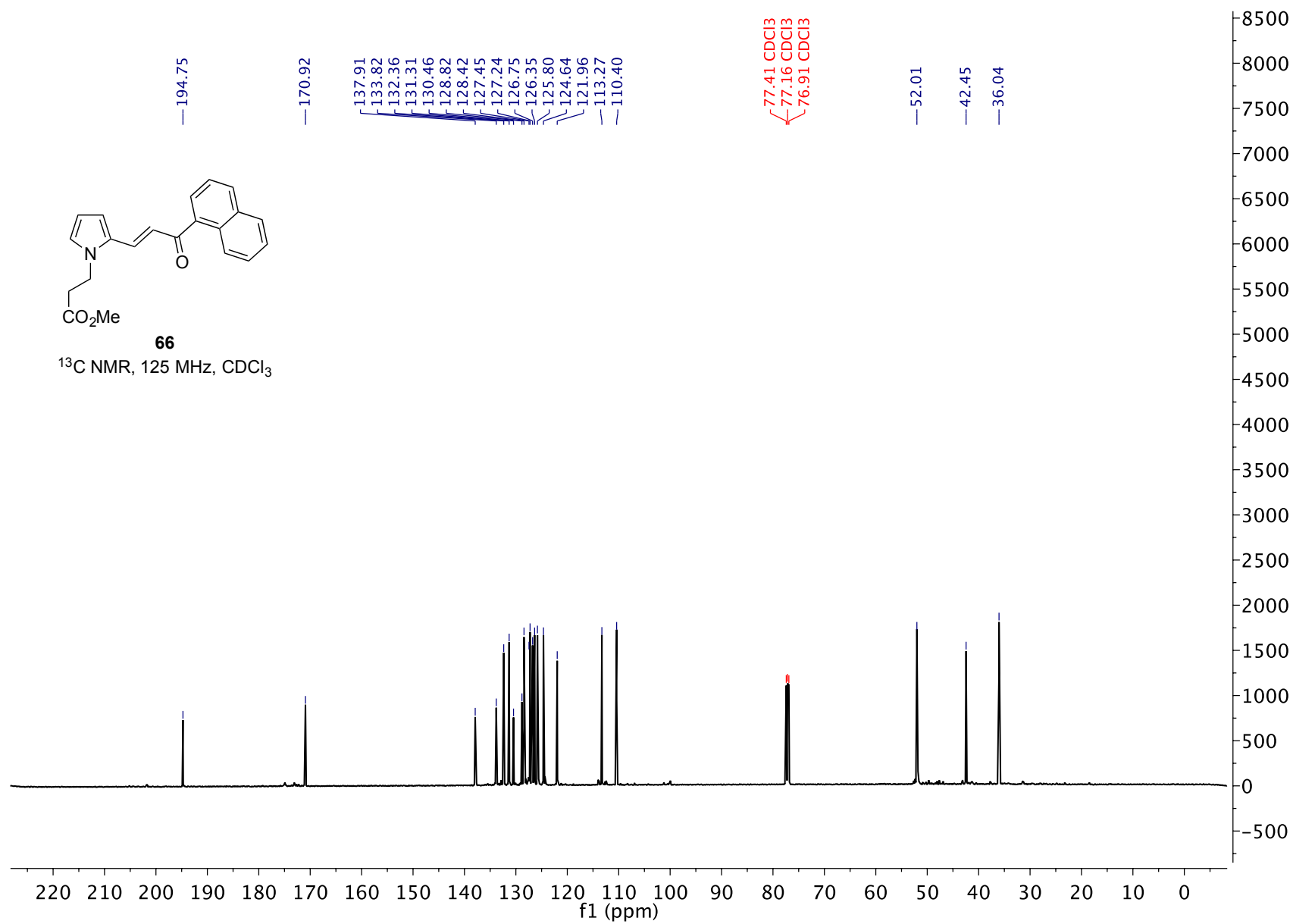


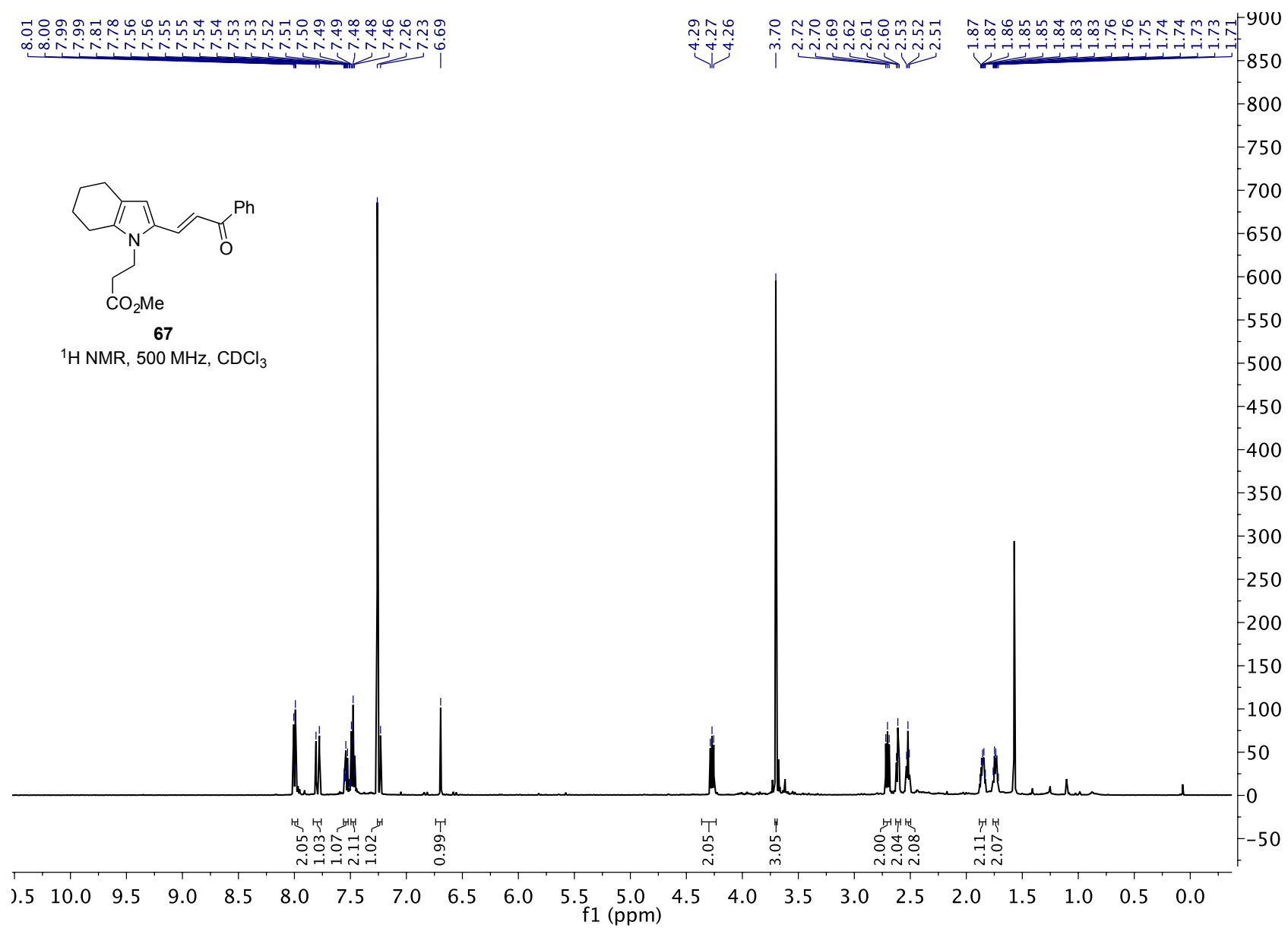


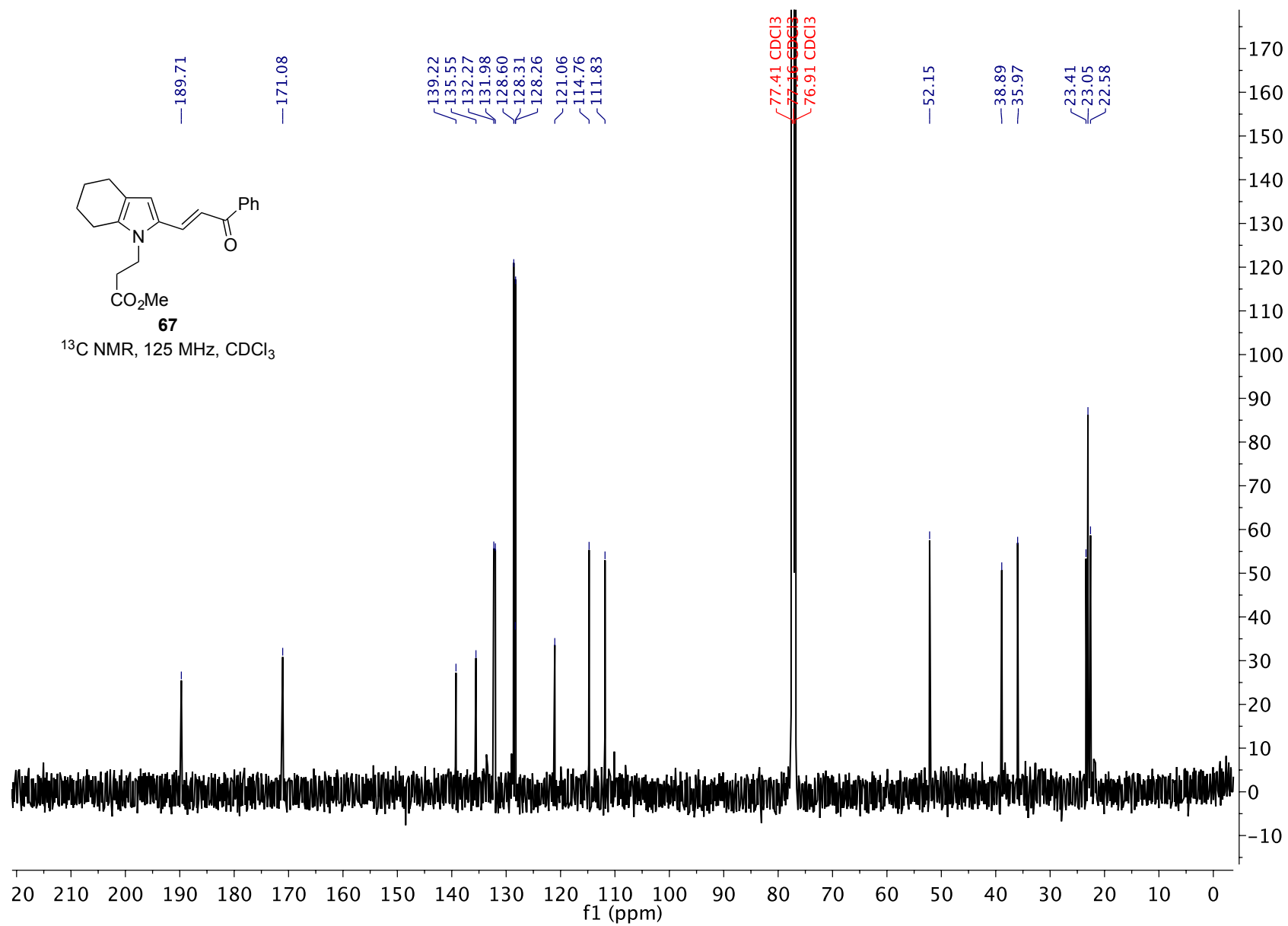


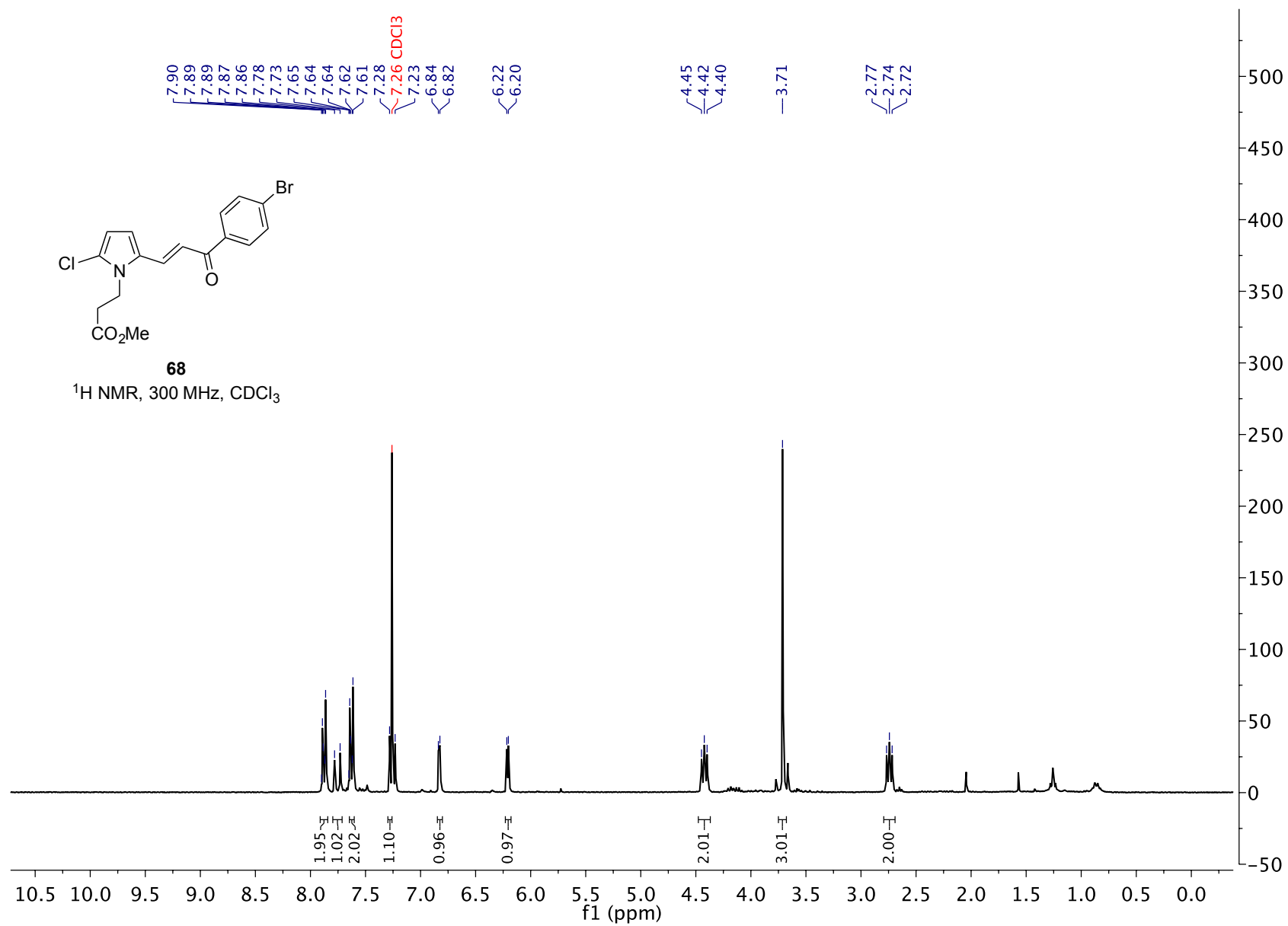


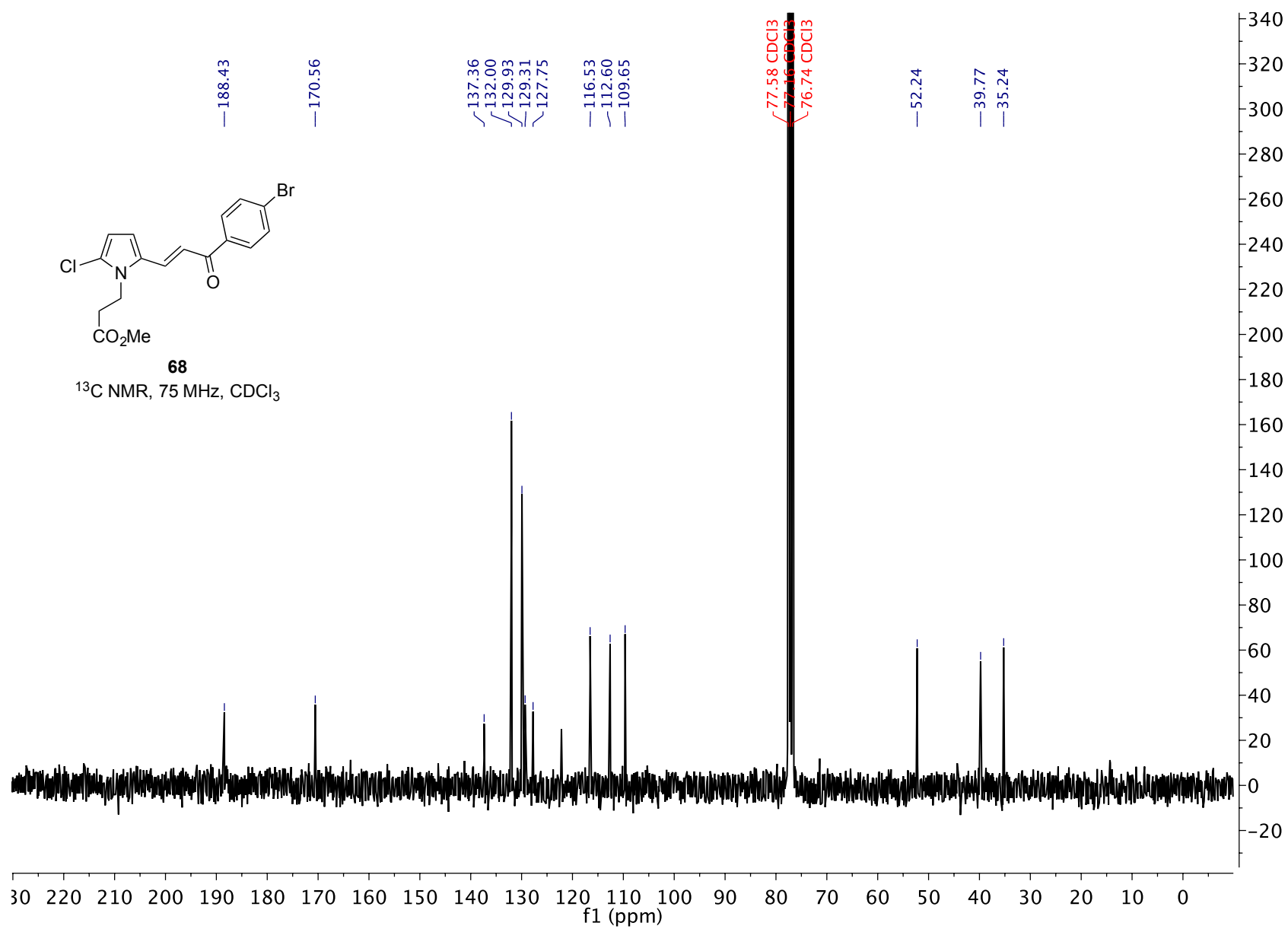


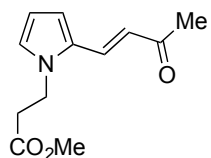






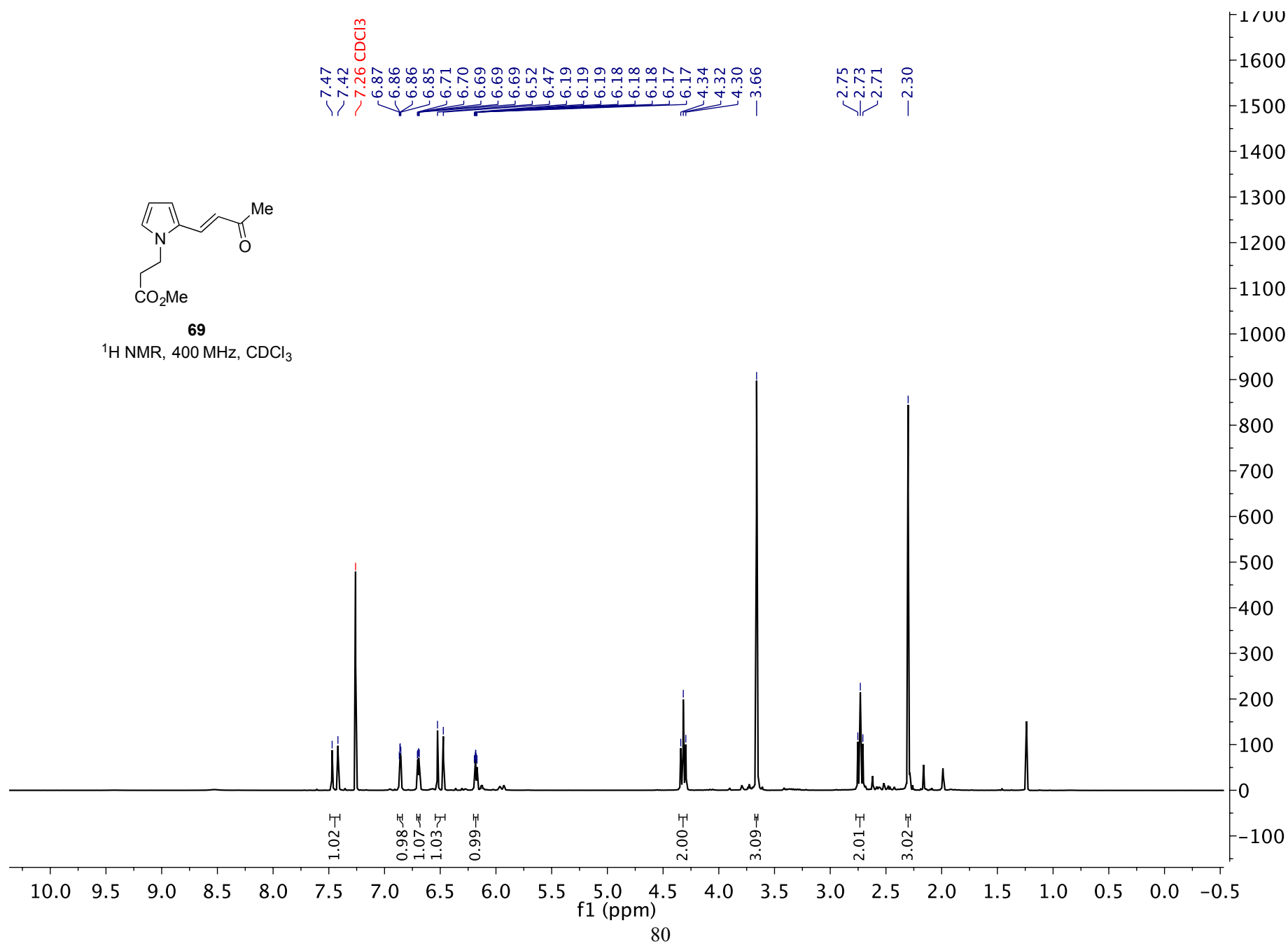


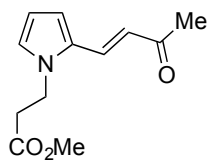




69

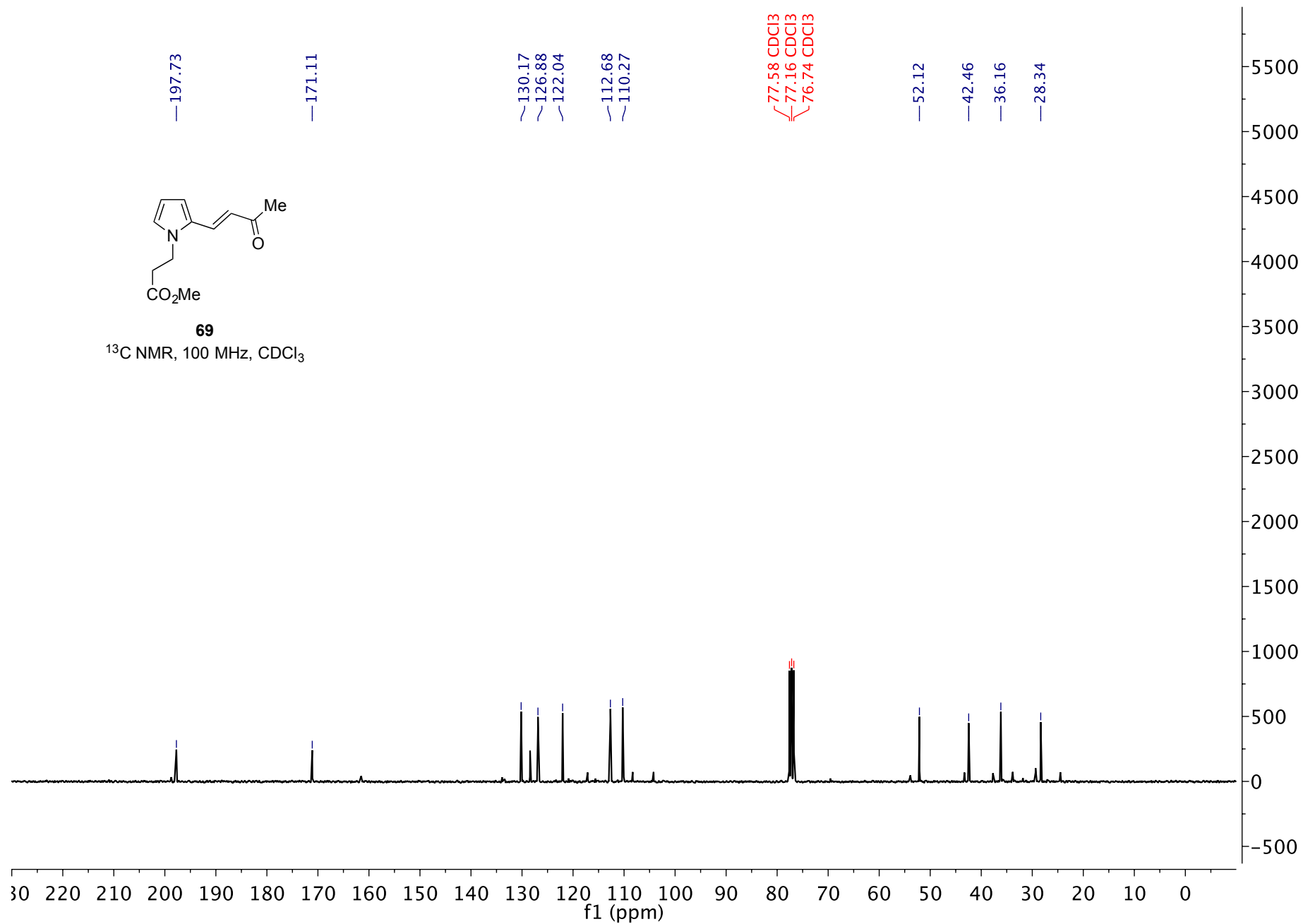
¹H NMR, 400 MHz, CDCl₃

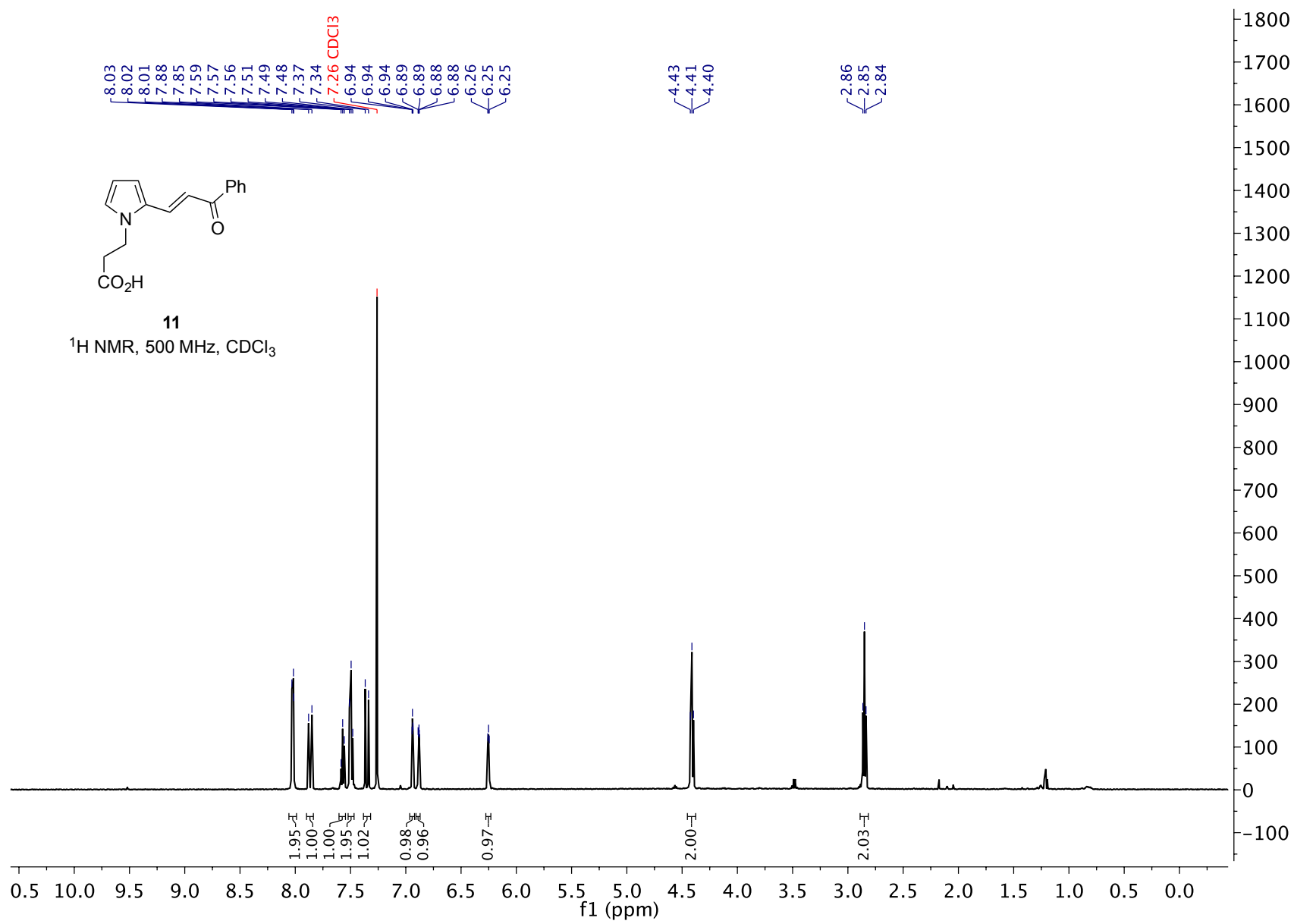


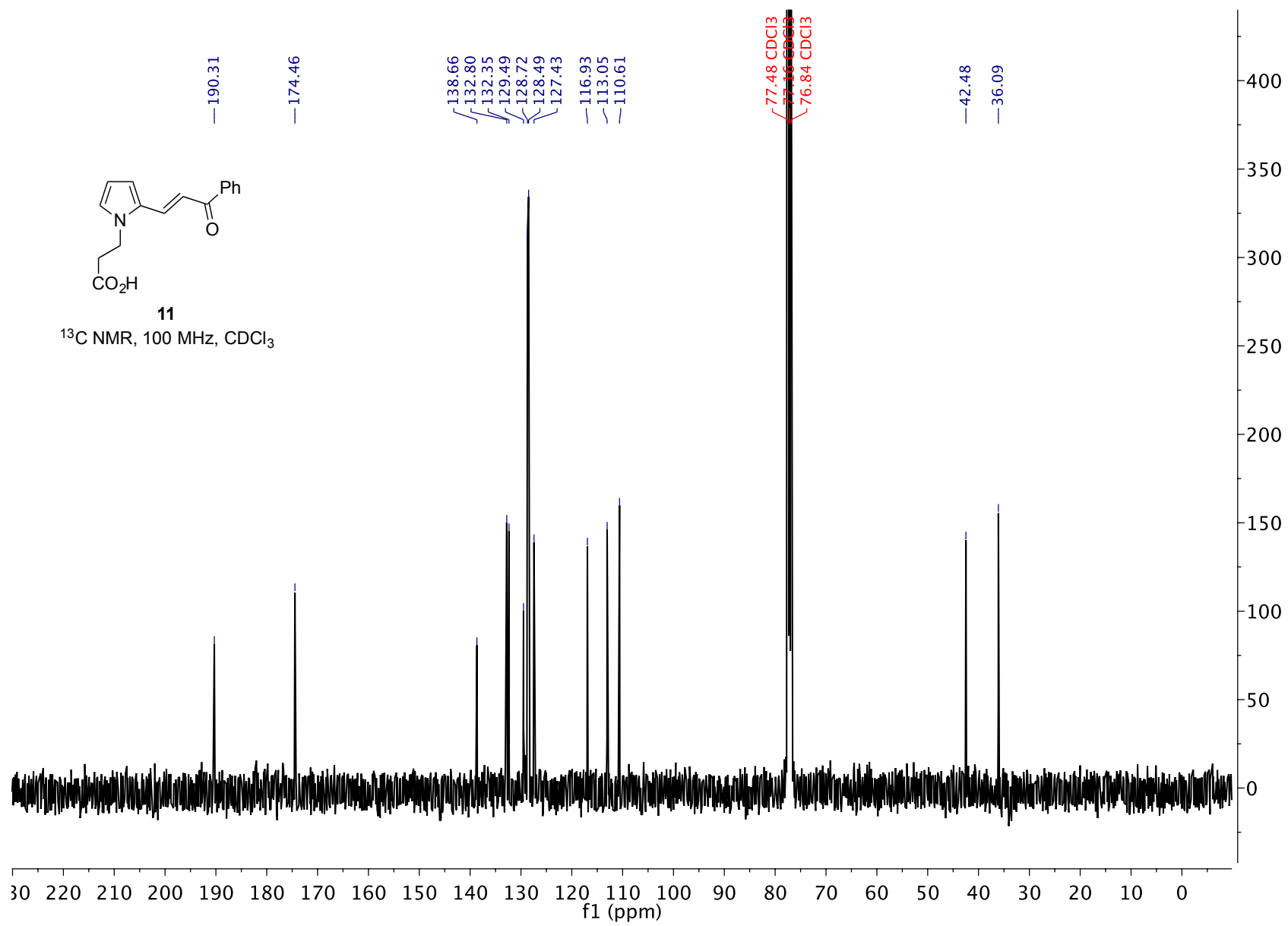


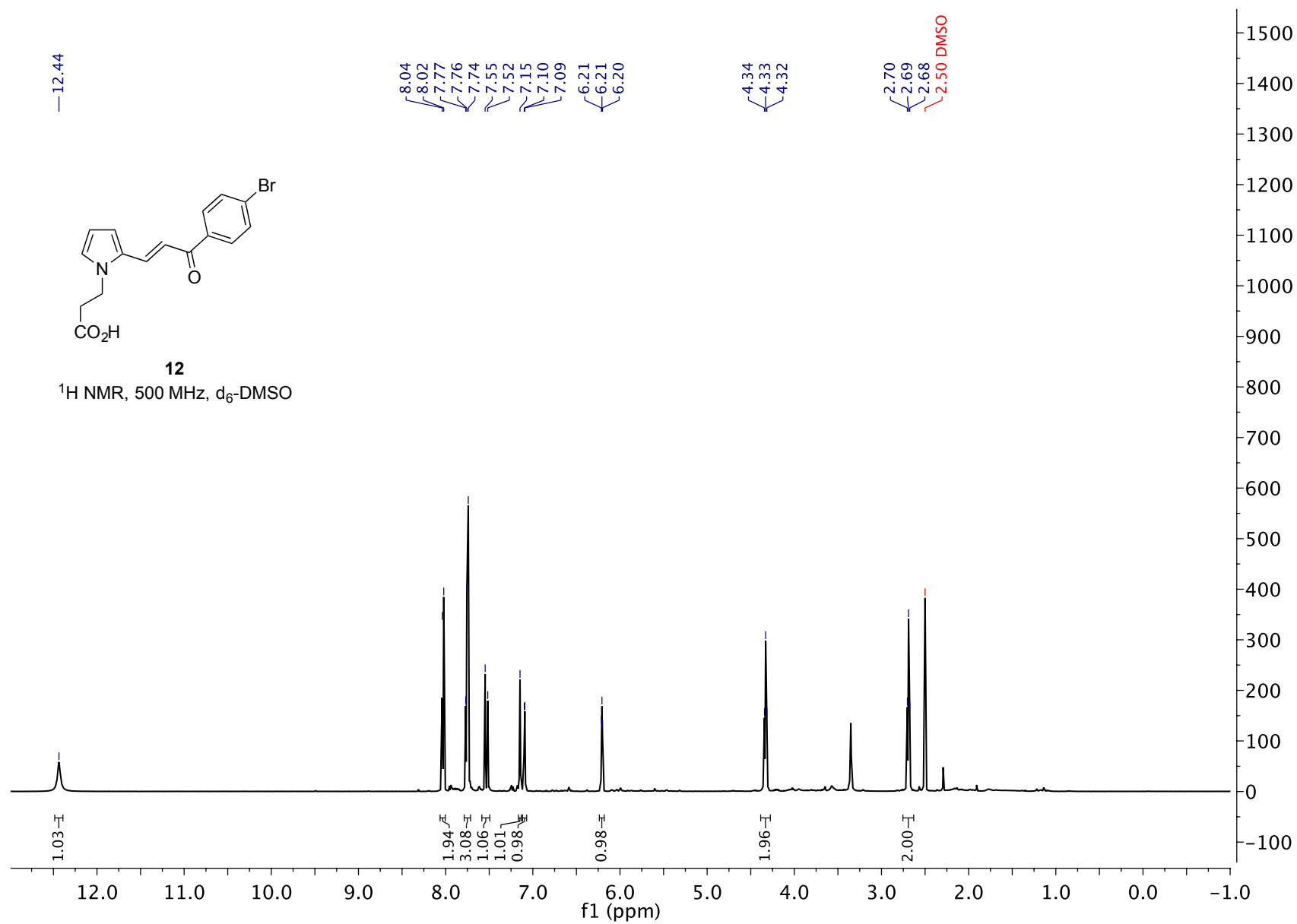
69

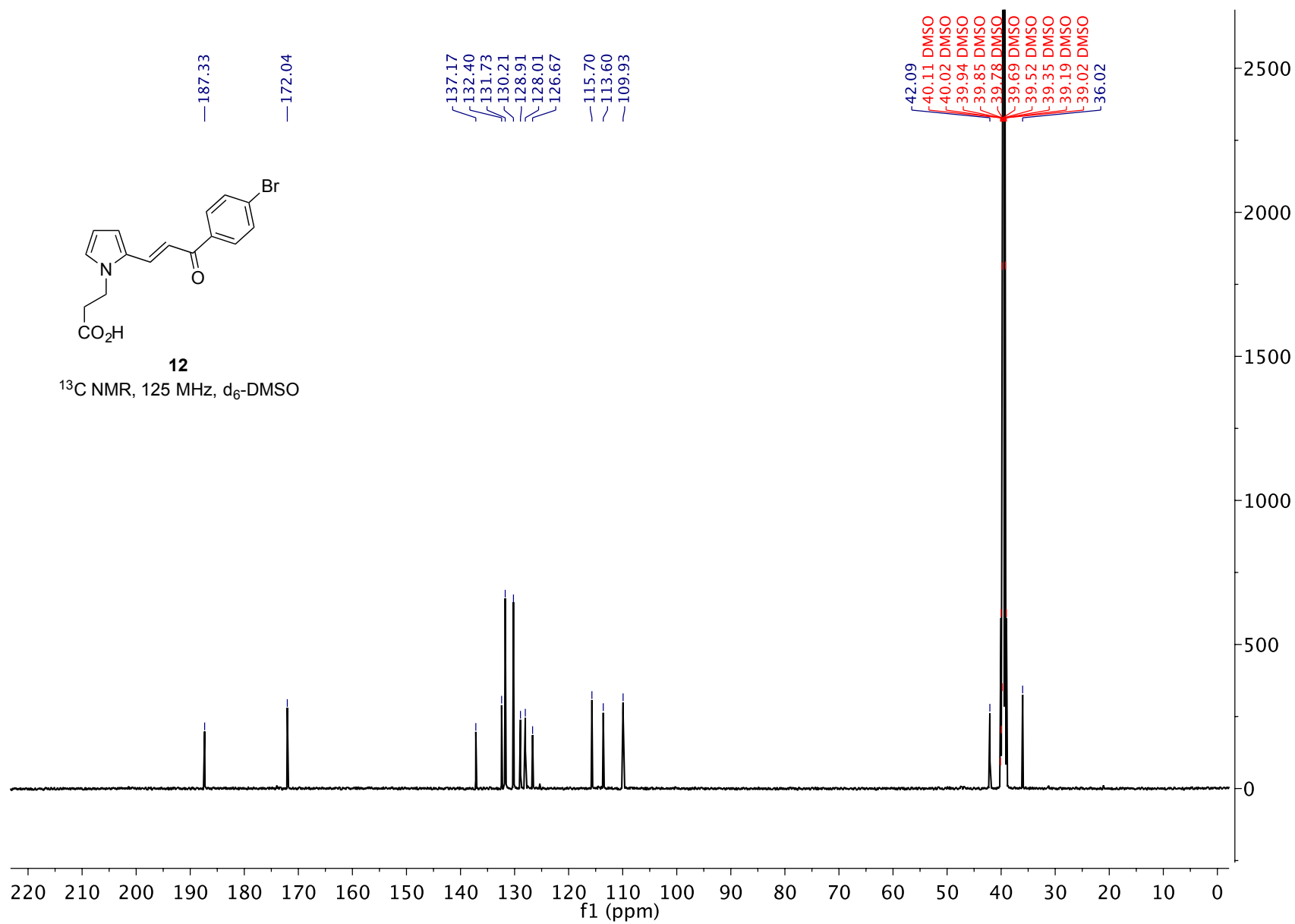
^{13}C NMR, 100 MHz, CDCl_3

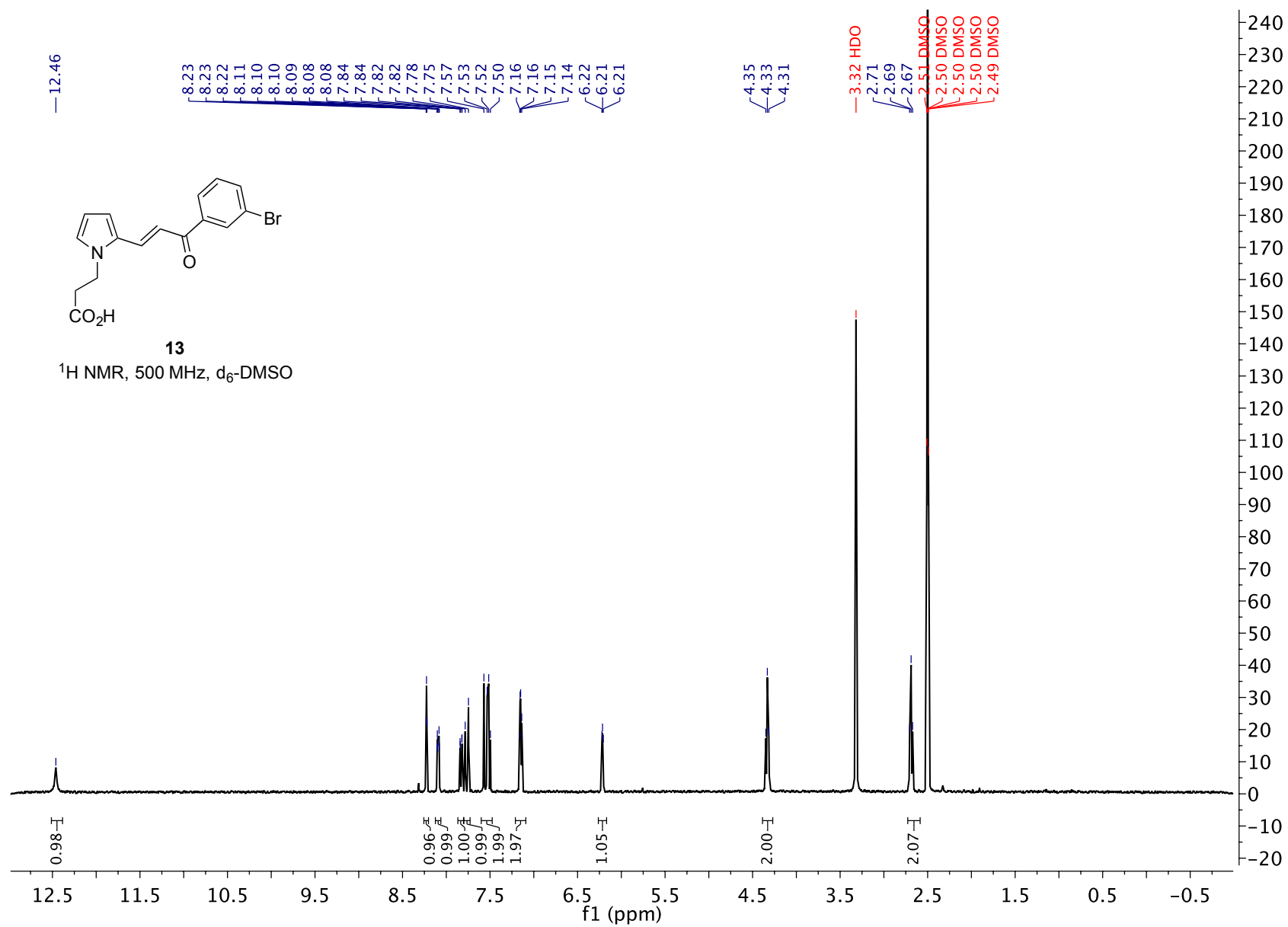


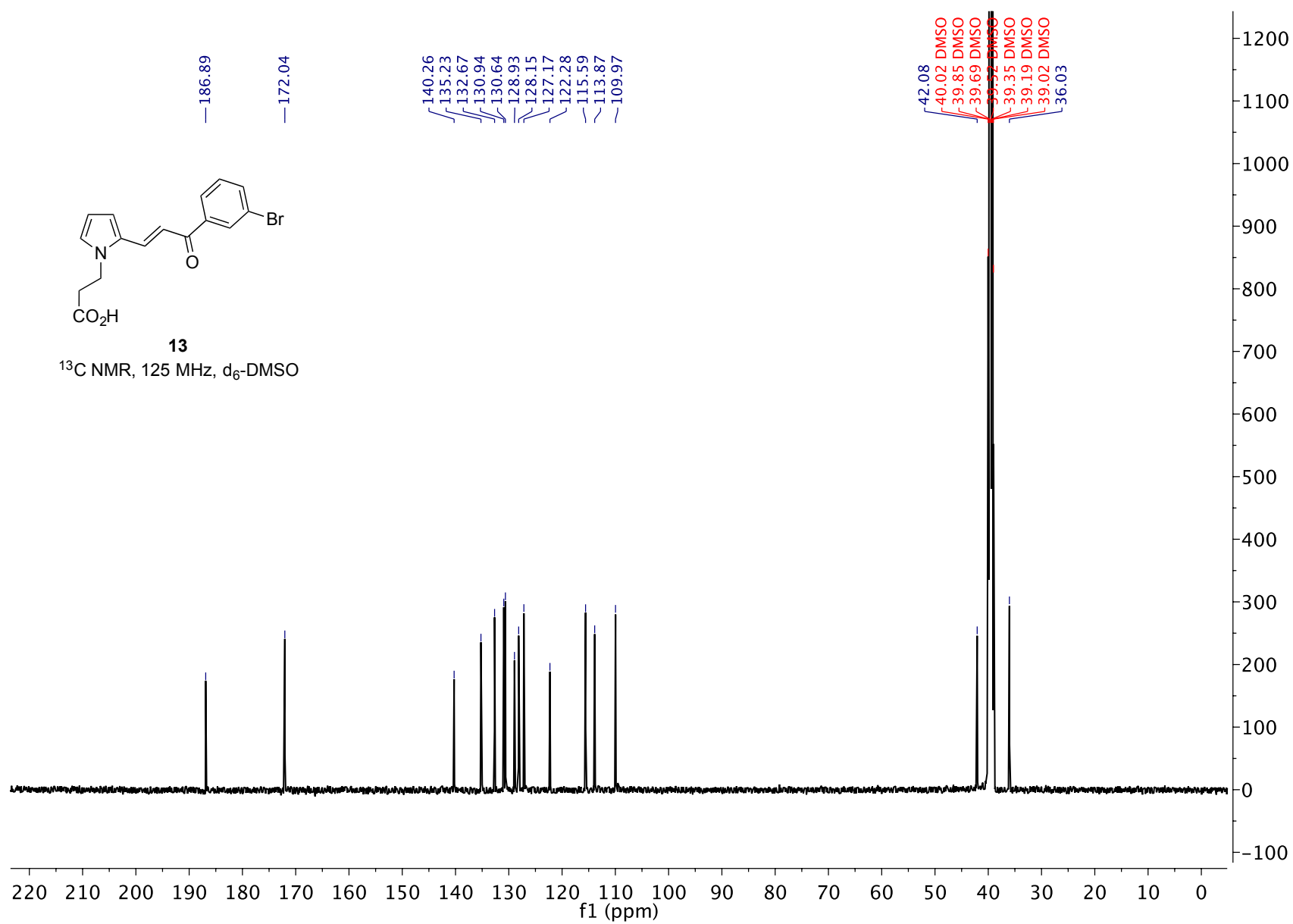


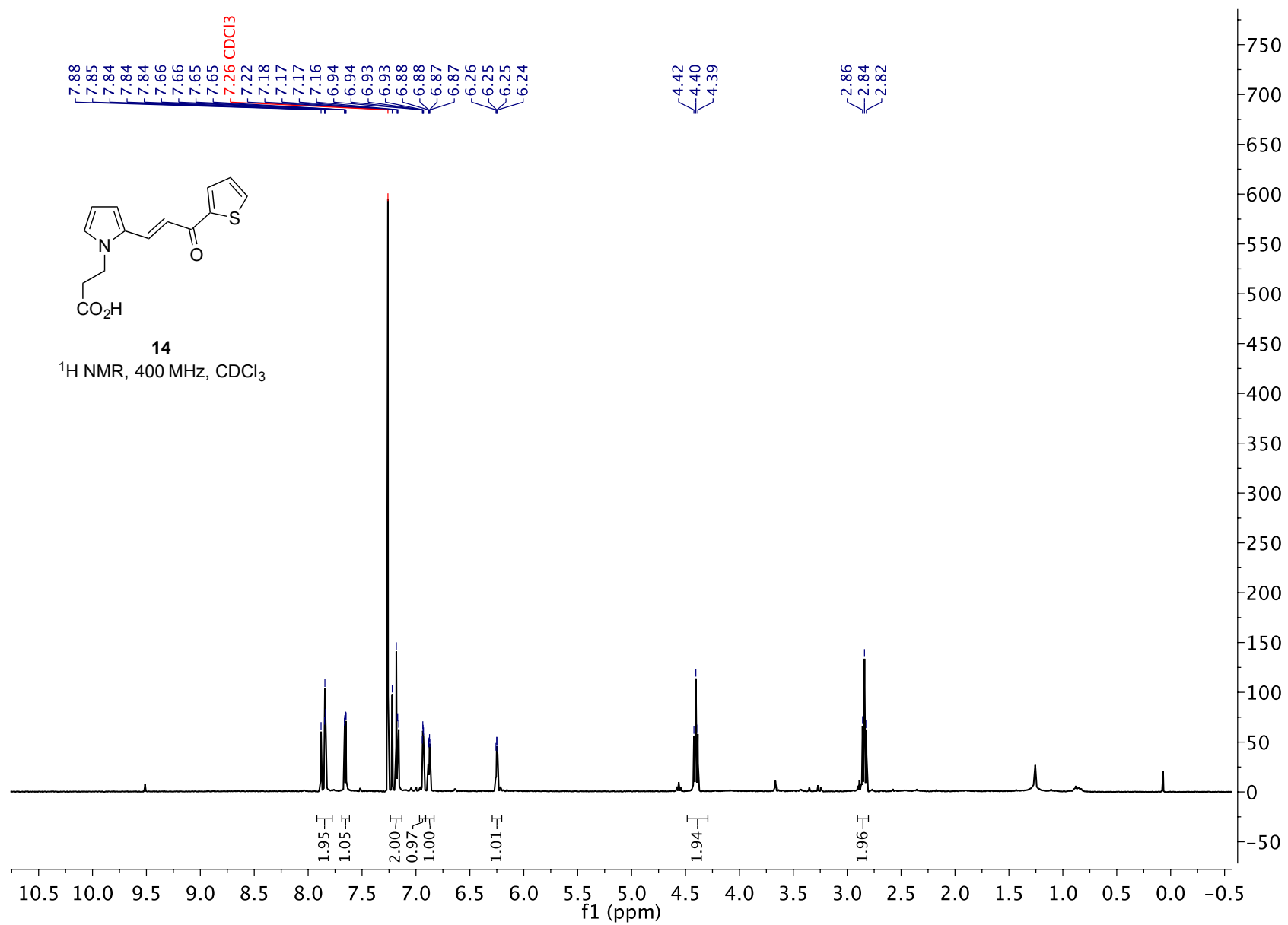


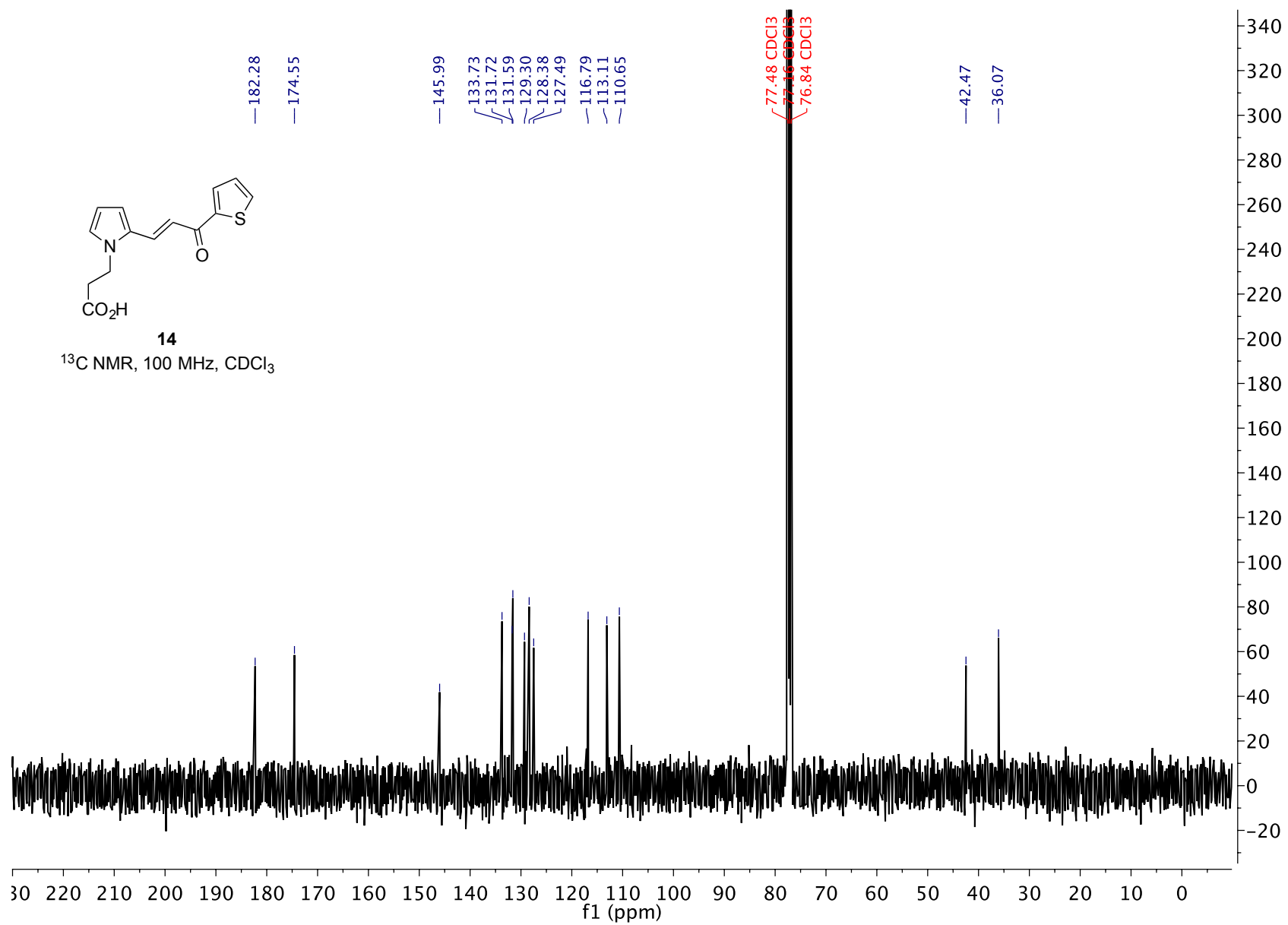


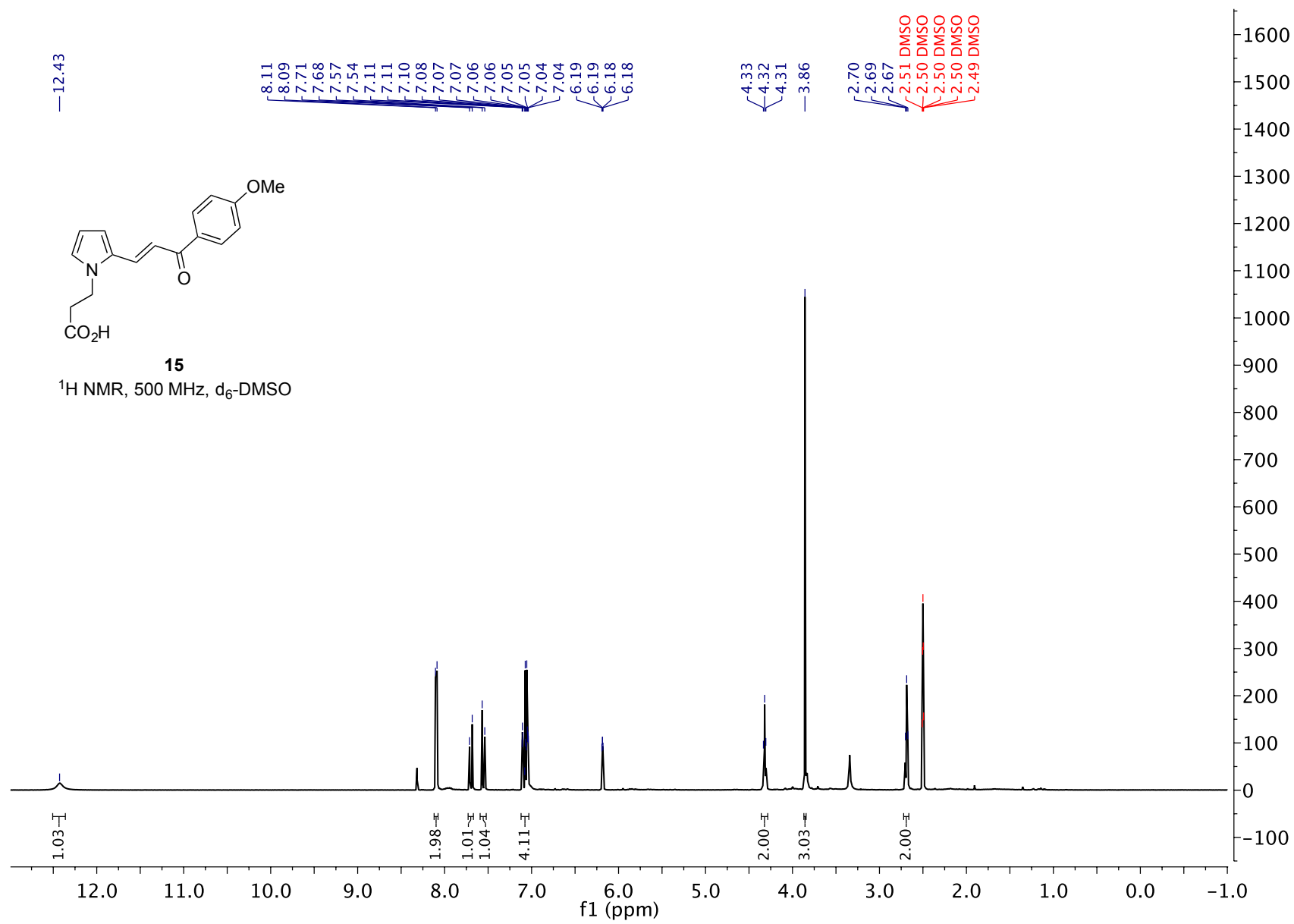


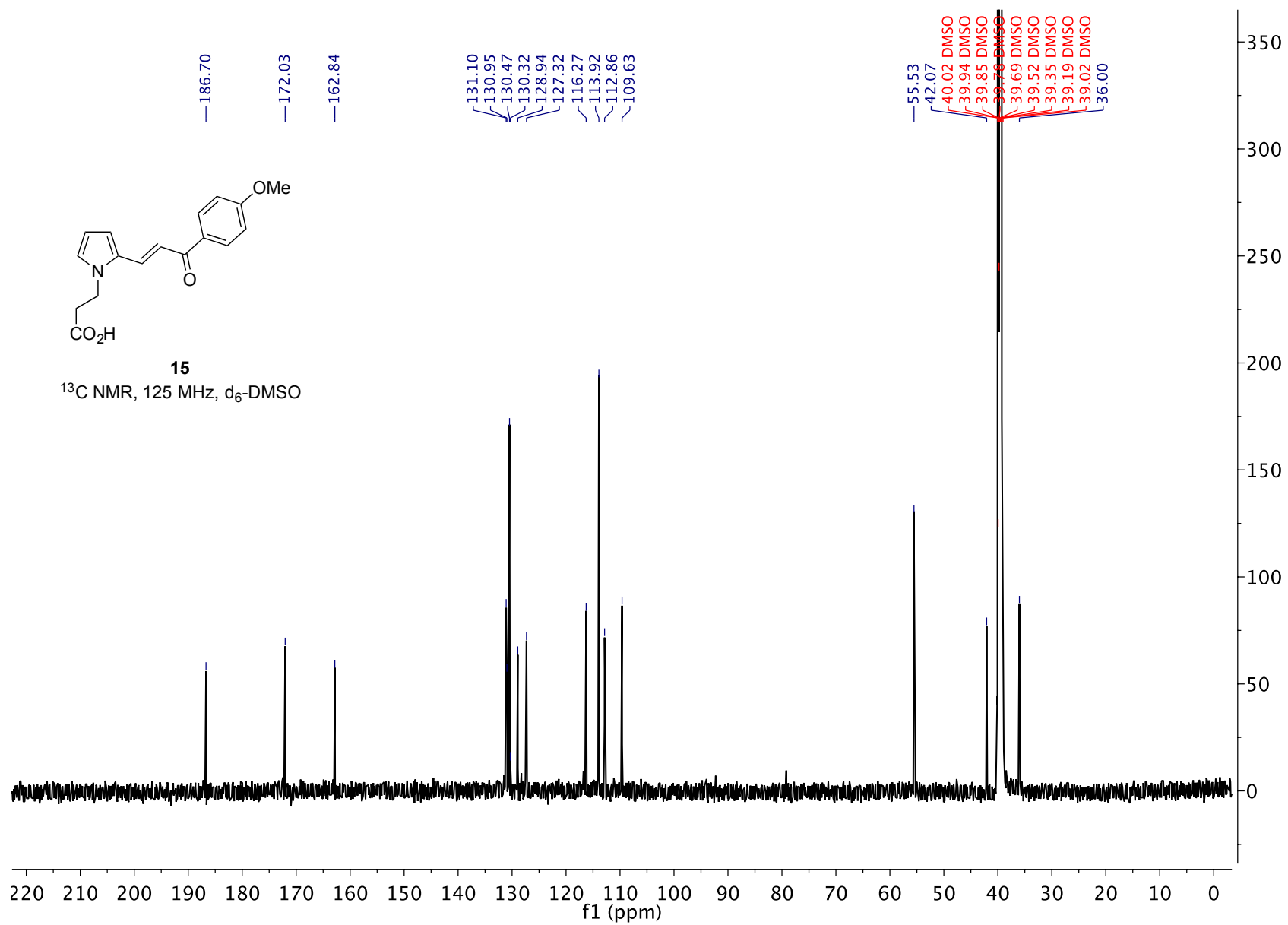


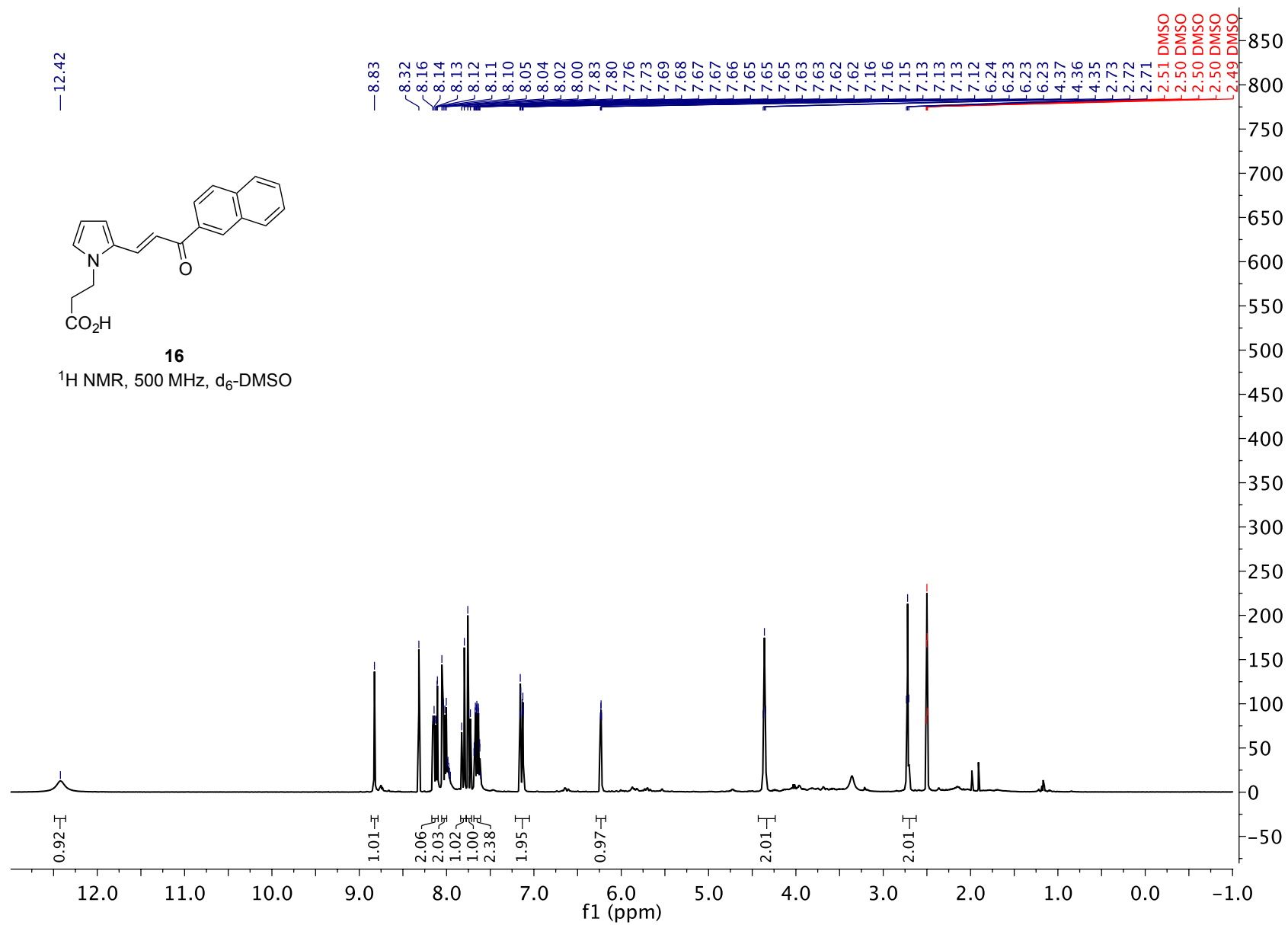


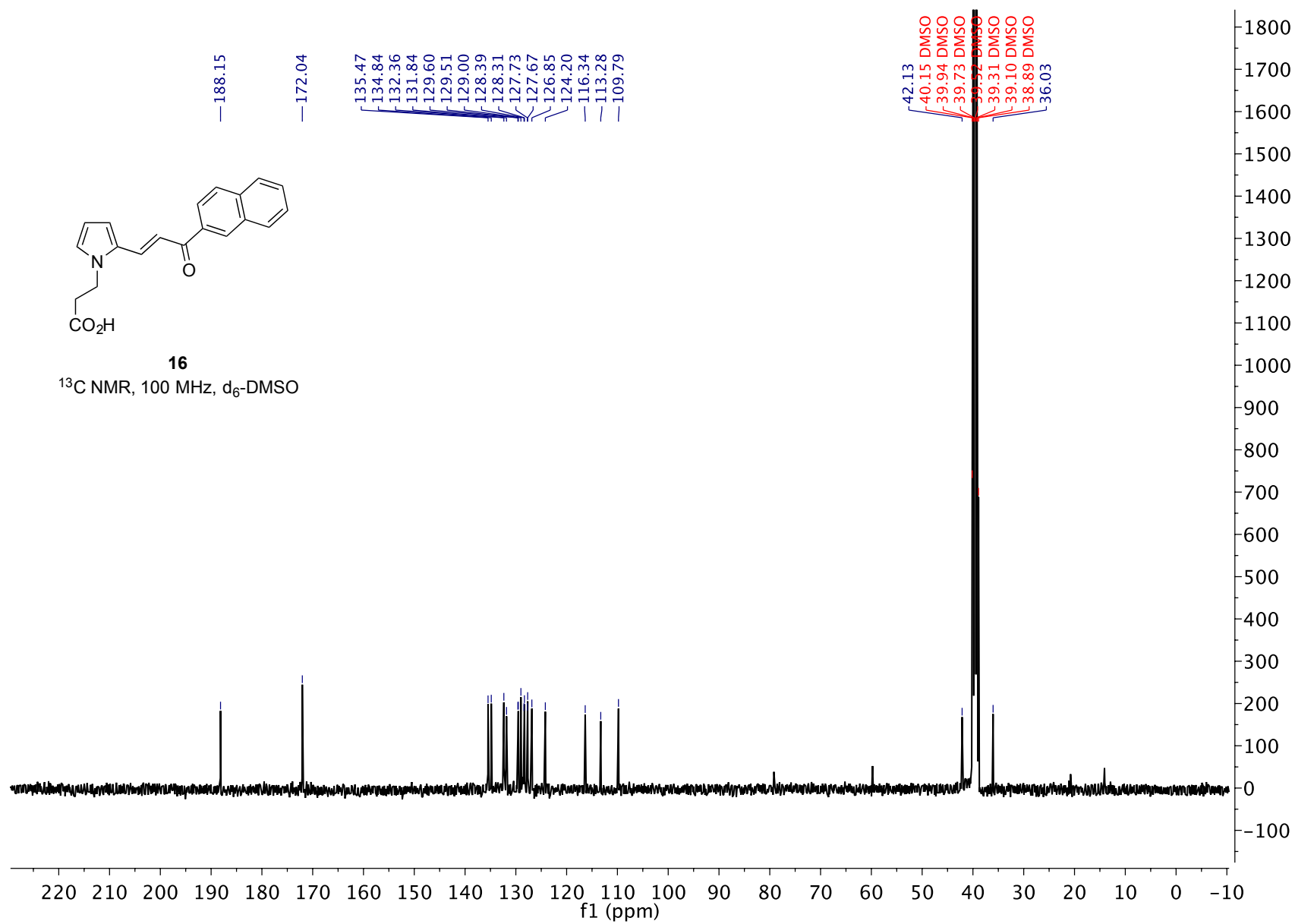


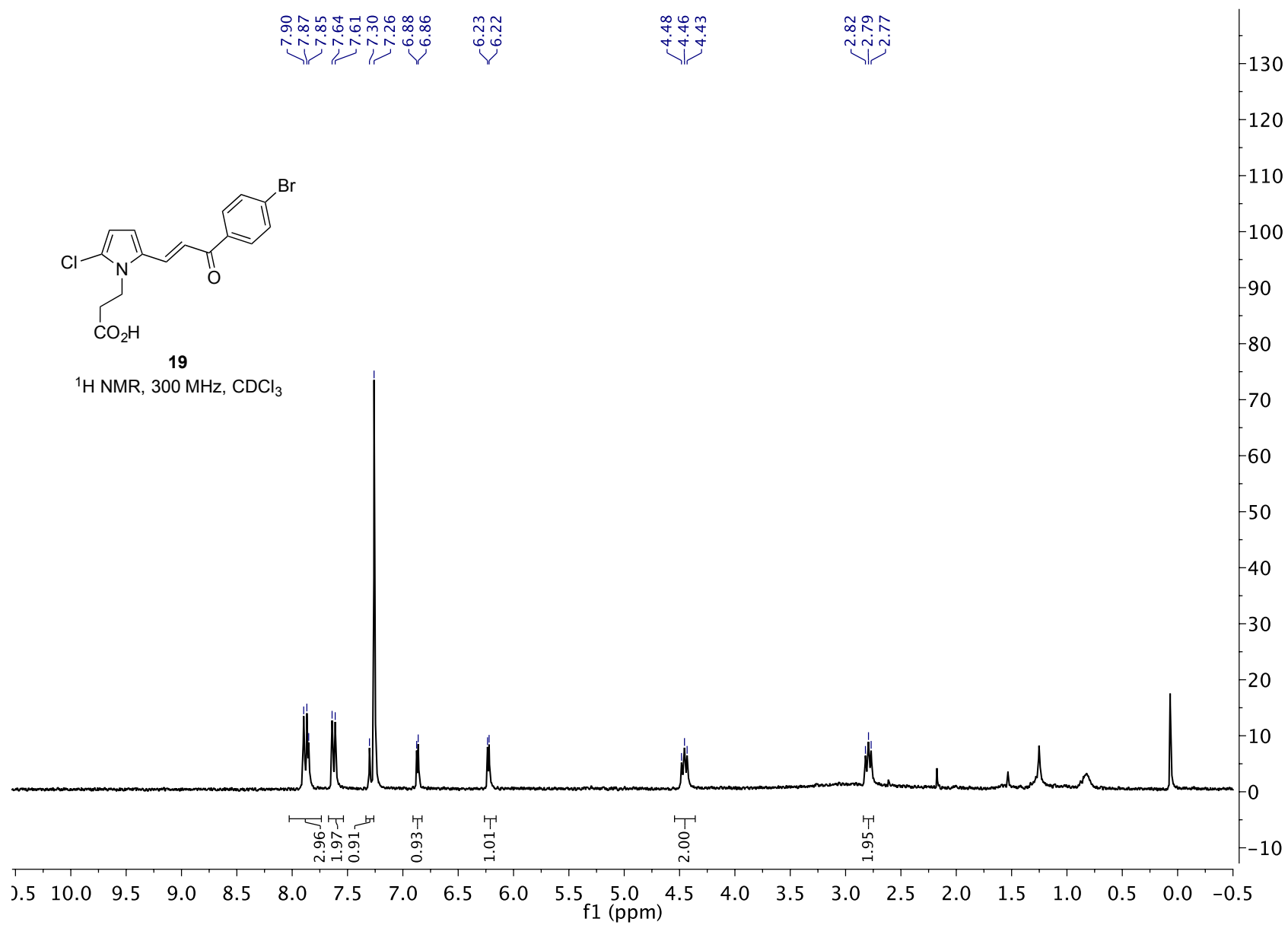


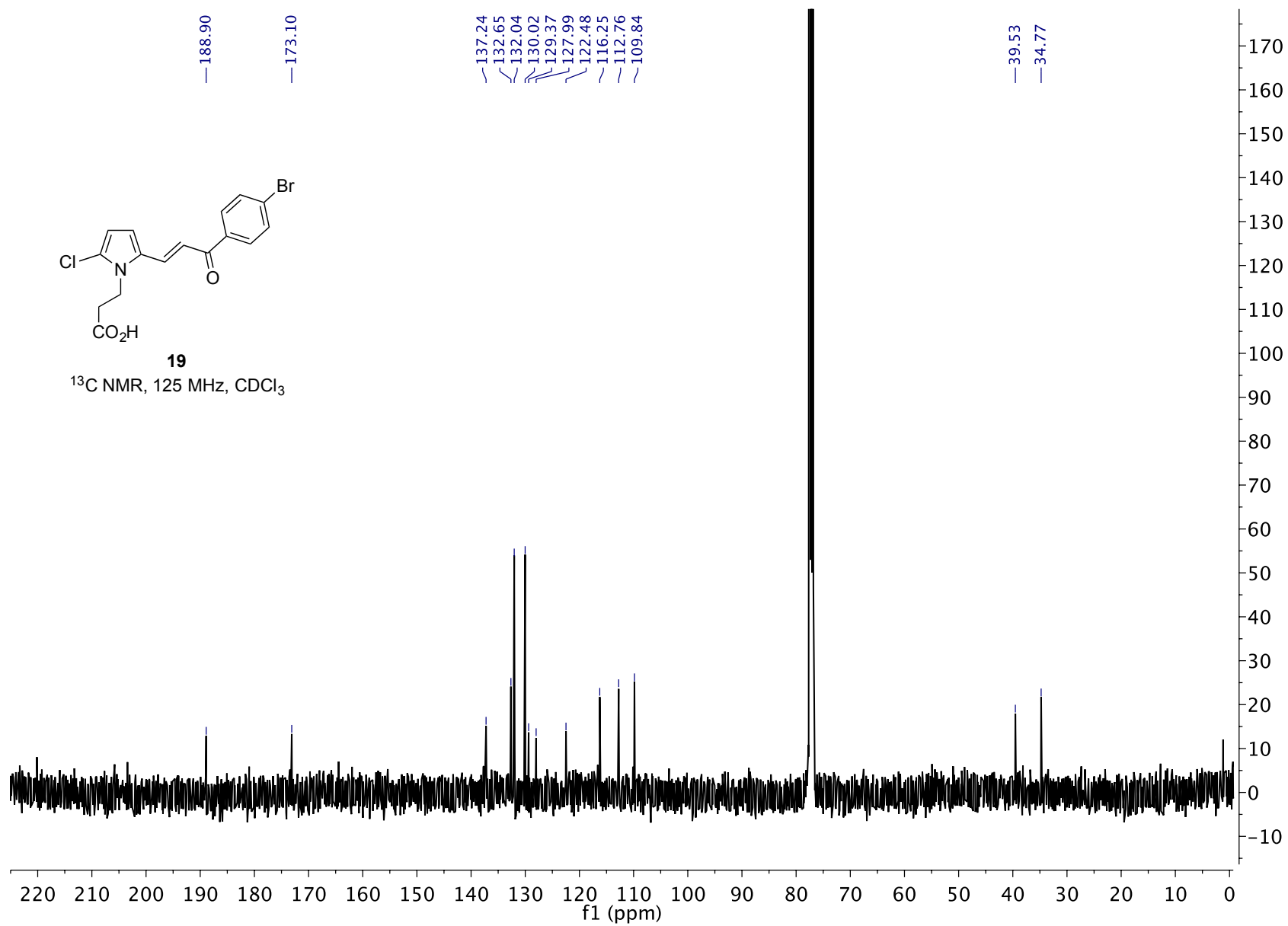


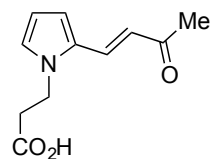






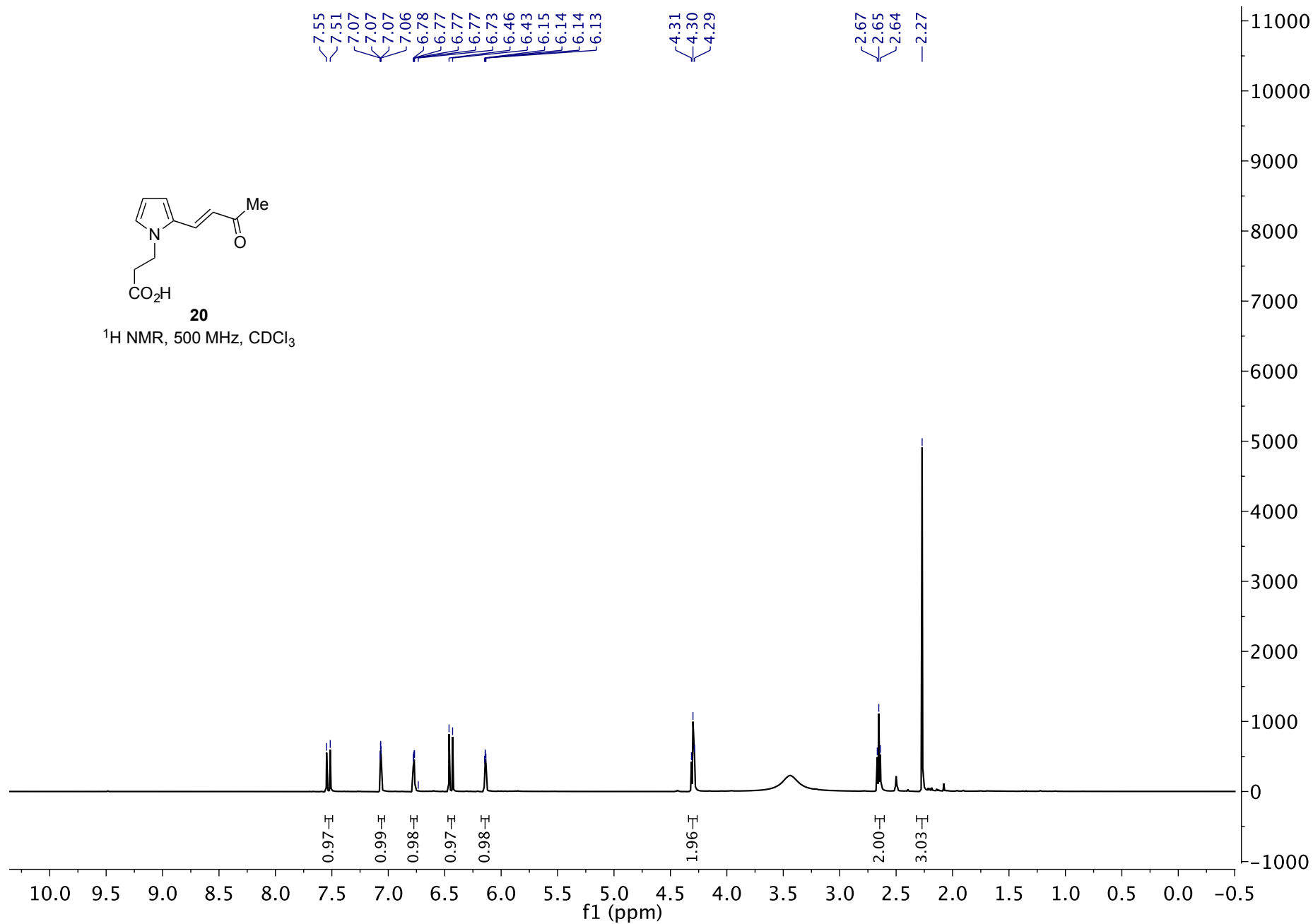


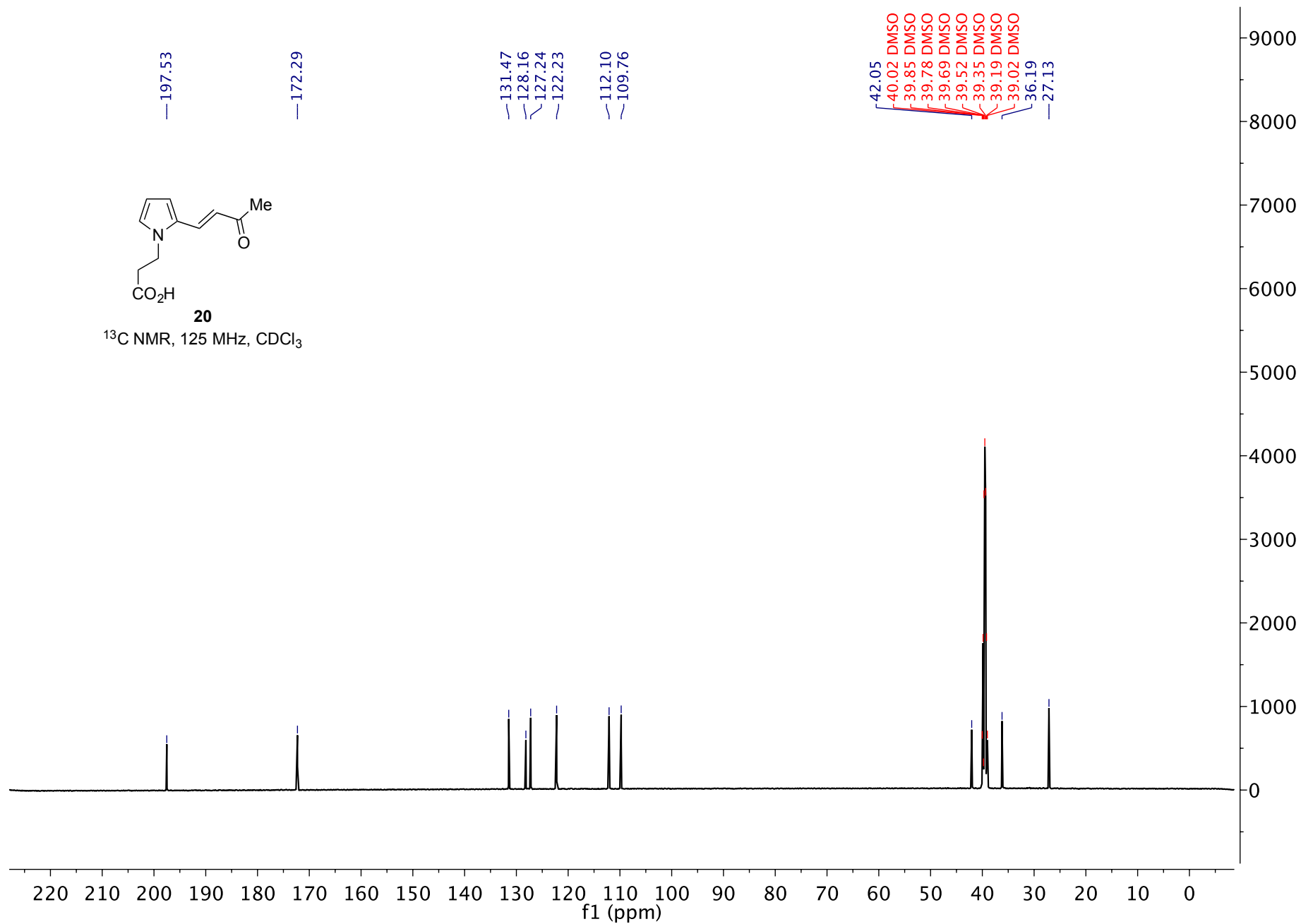
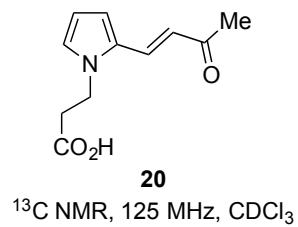


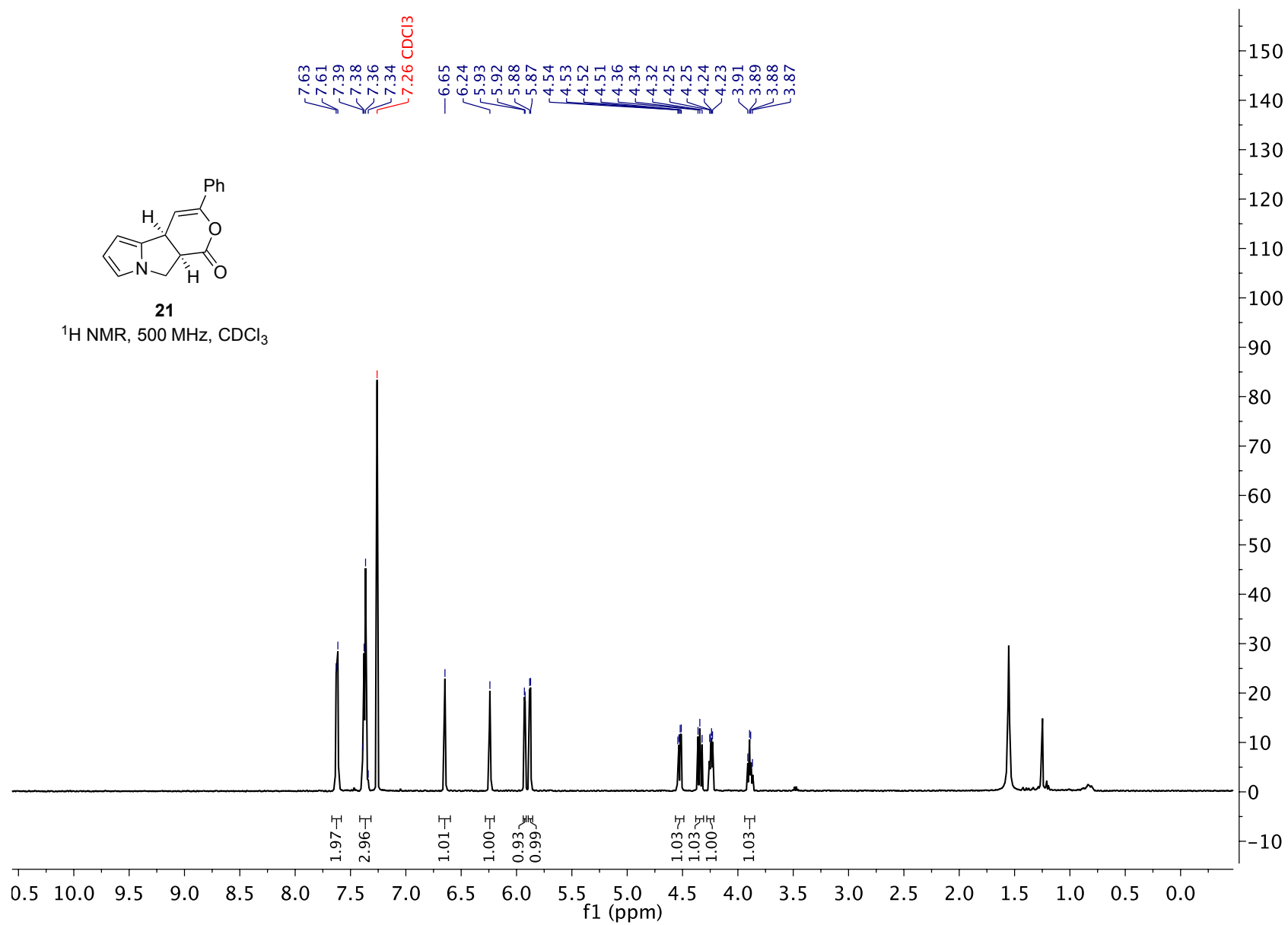


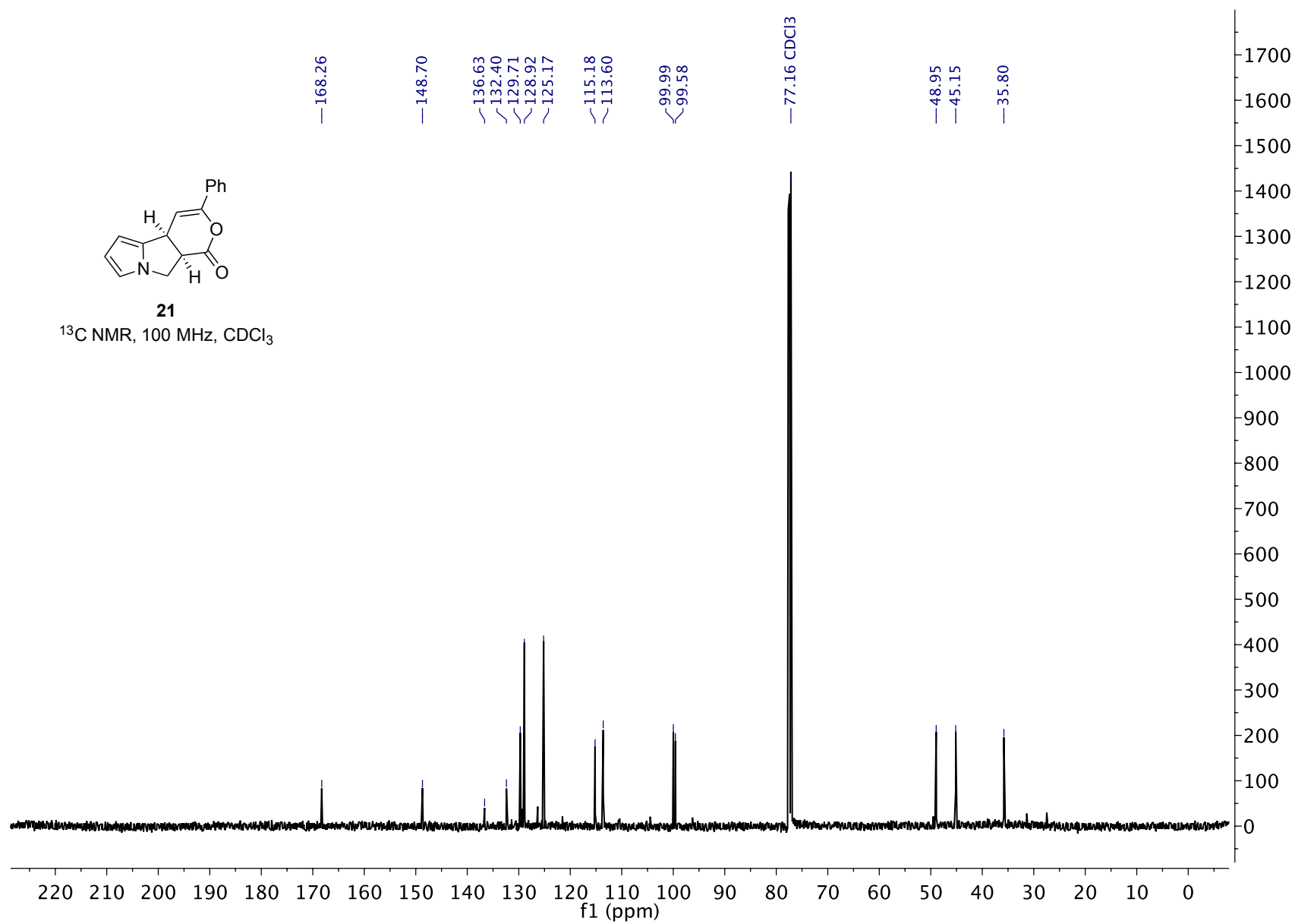
20

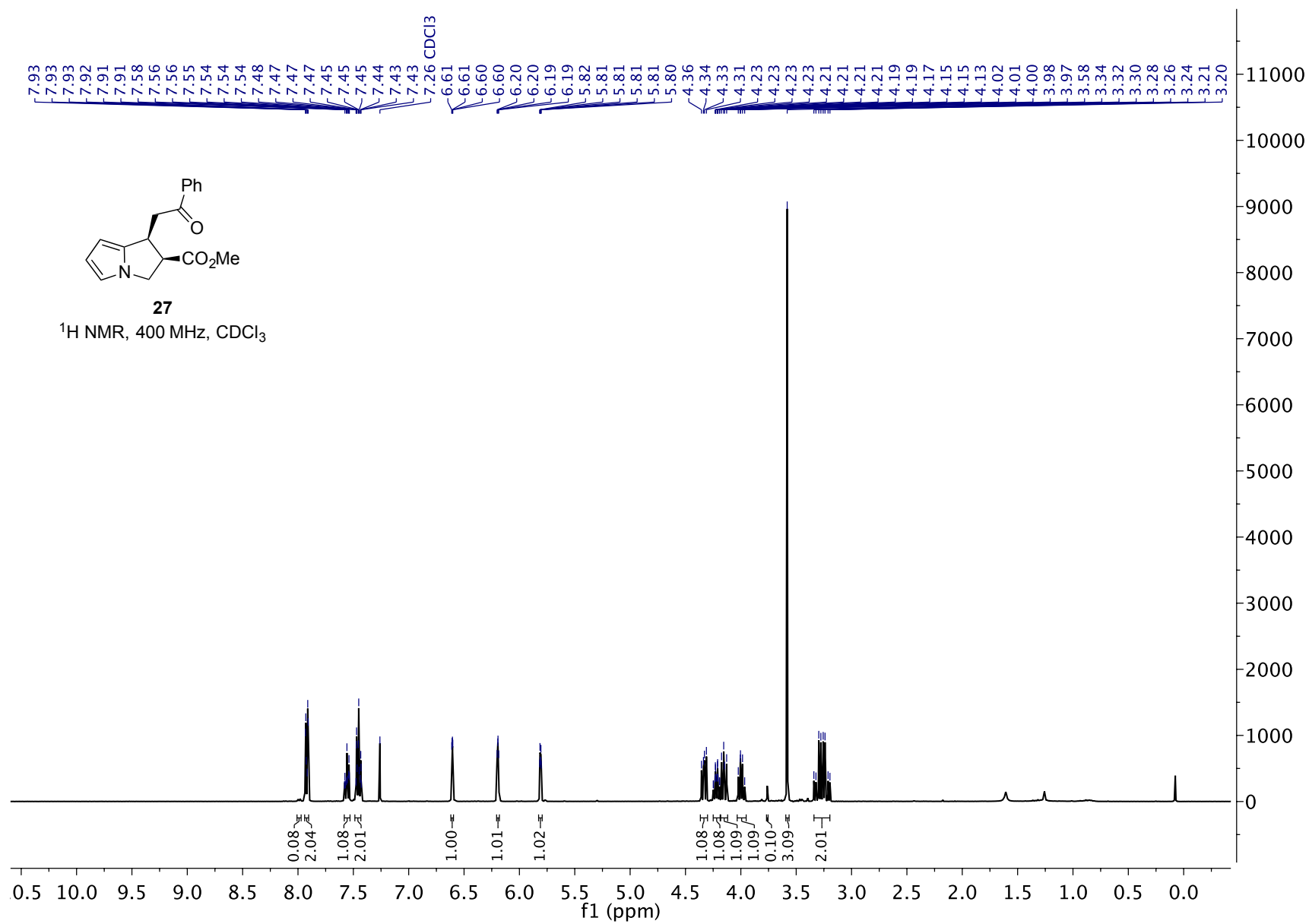
^1H NMR, 500 MHz, CDCl_3

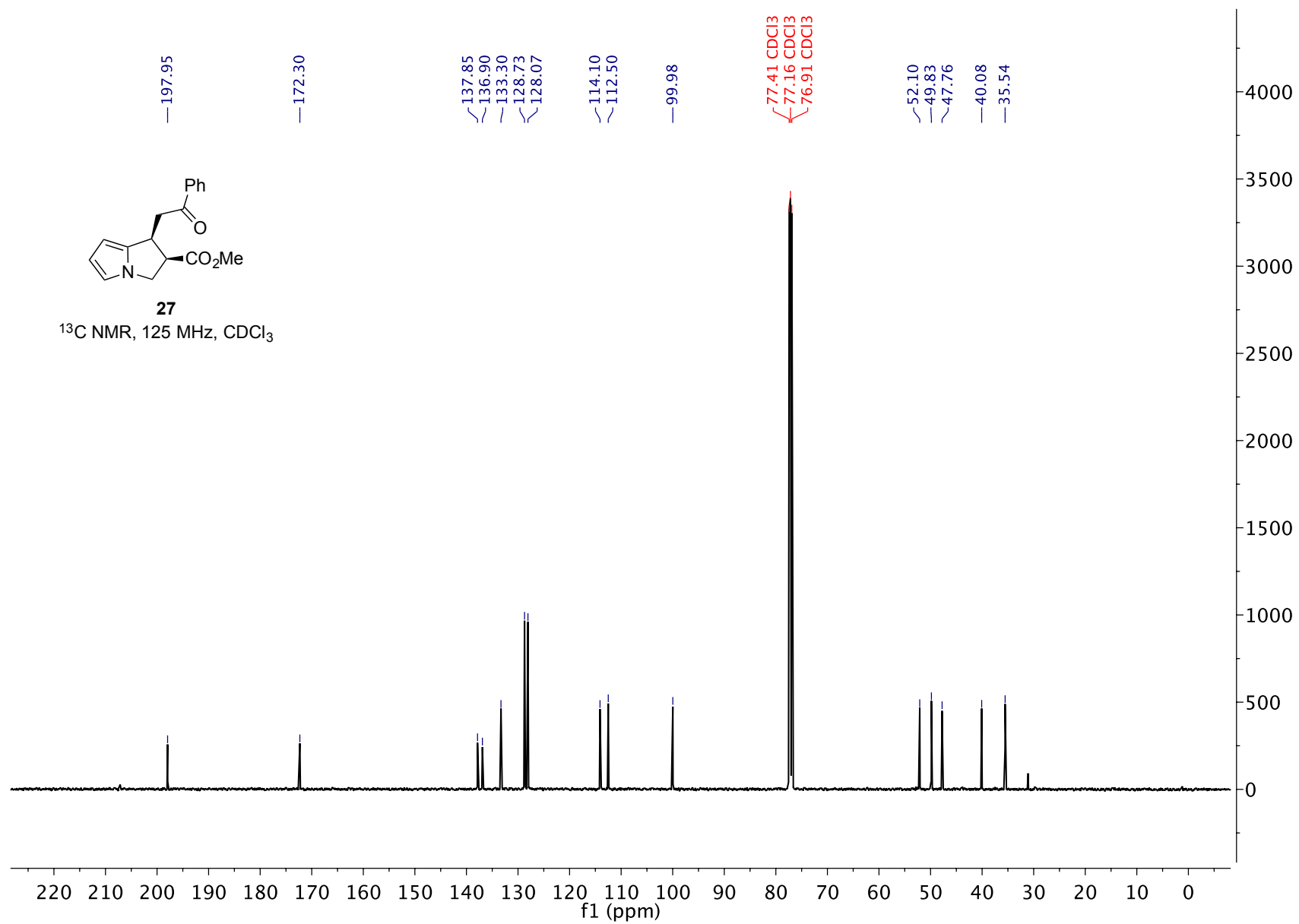


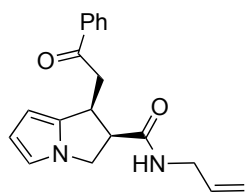






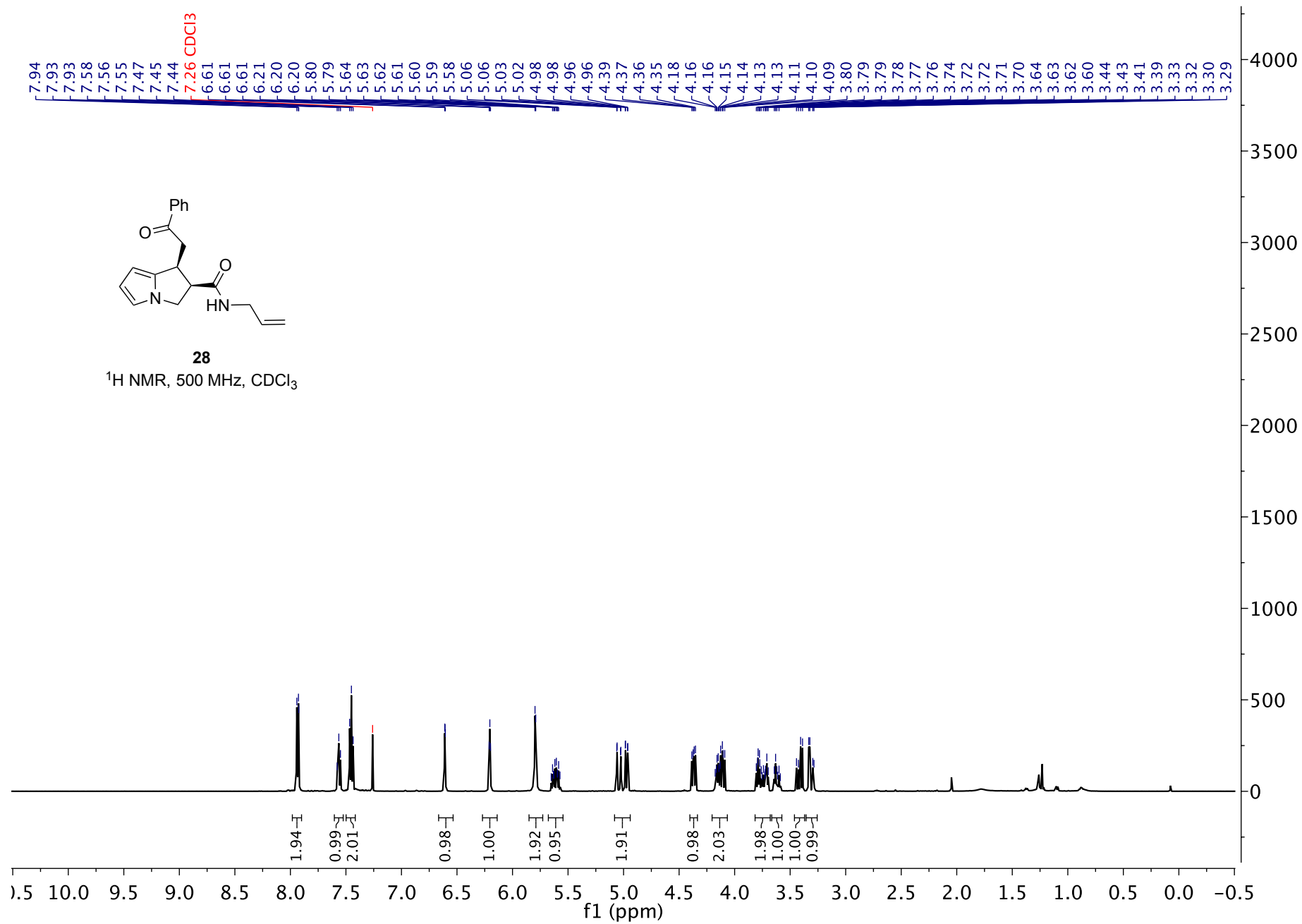


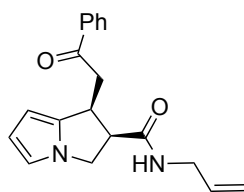




28

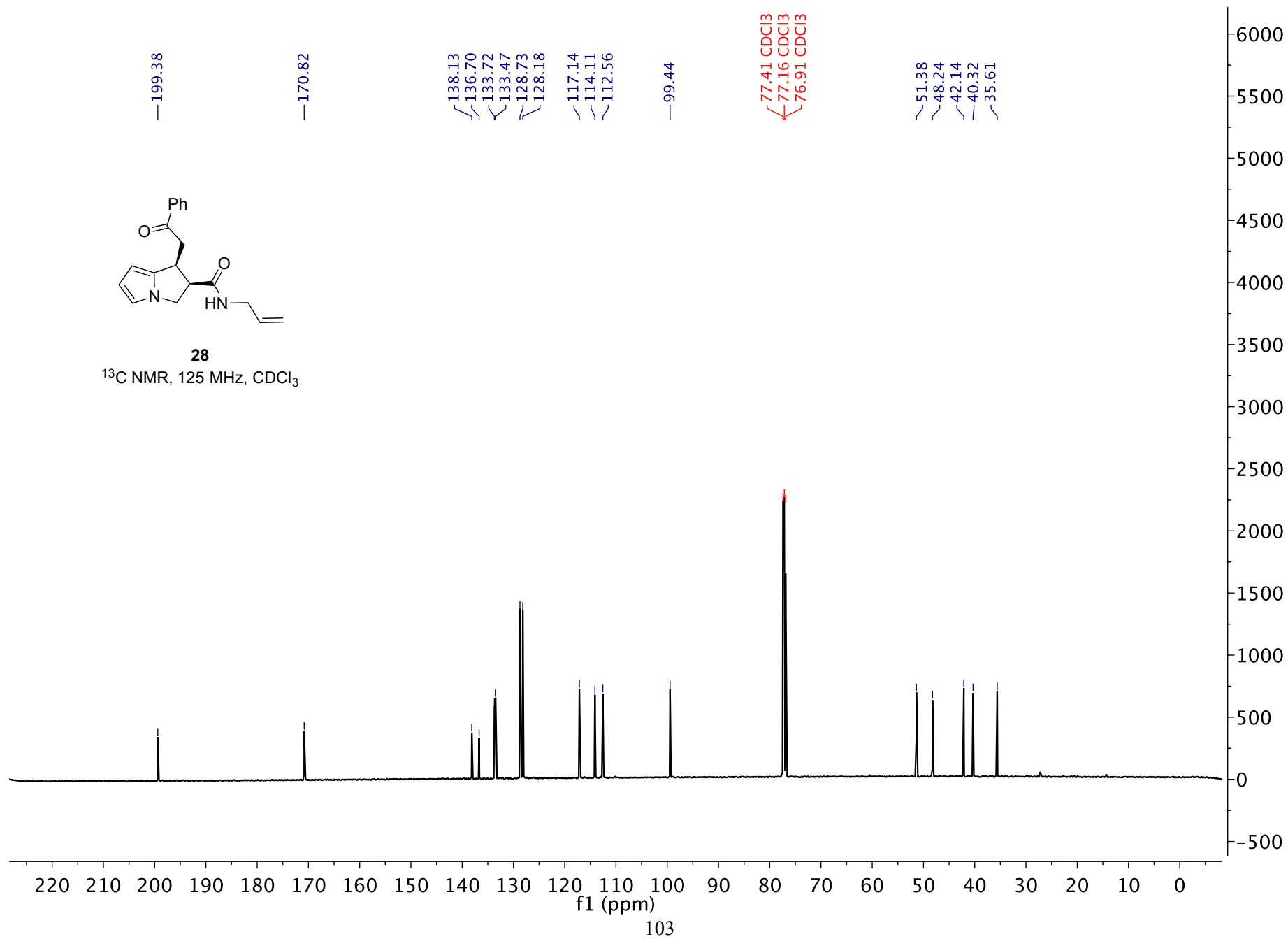
¹H NMR, 500 MHz, CDCl₃

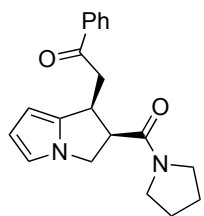




28

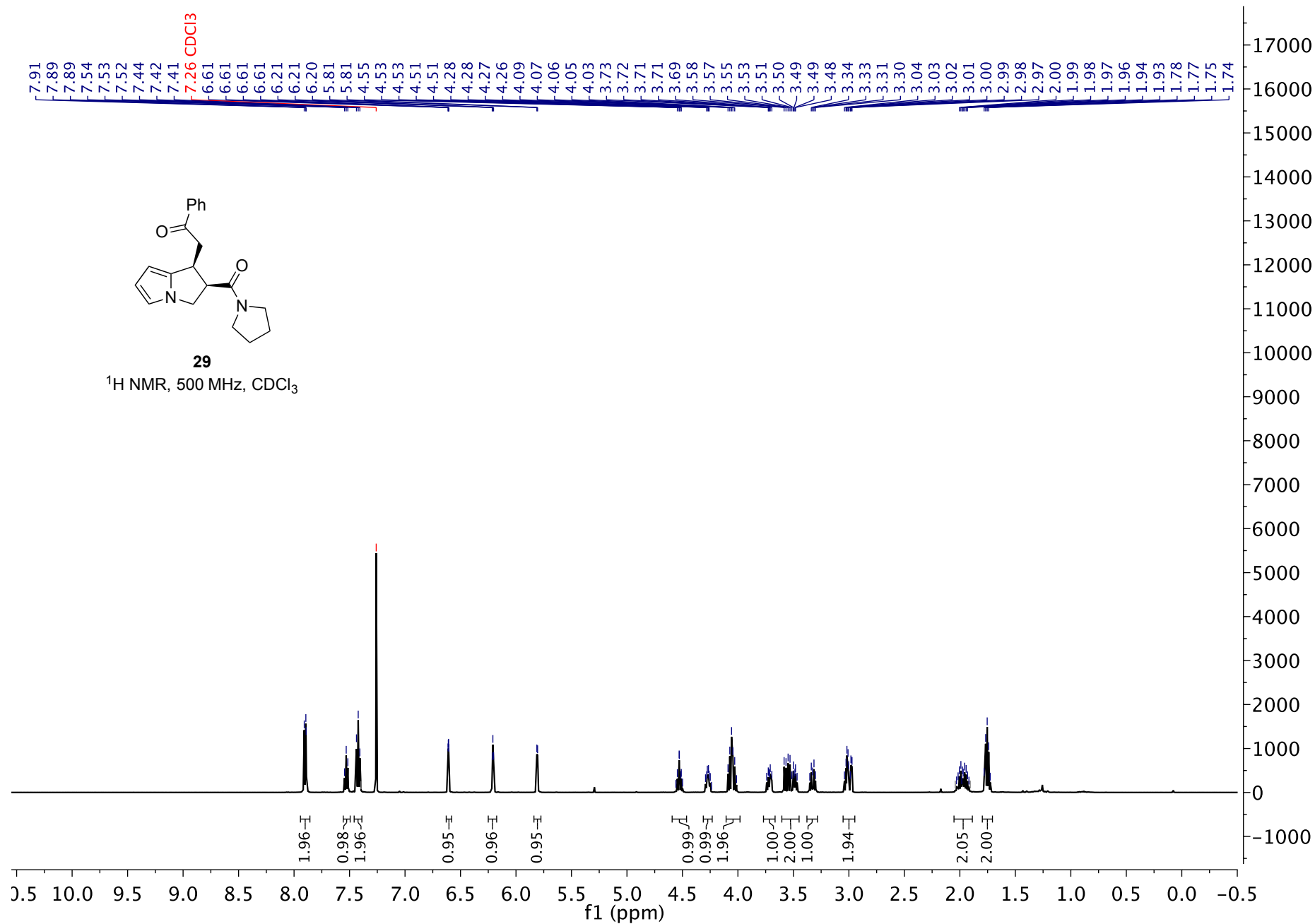
^{13}C NMR, 125 MHz, CDCl_3

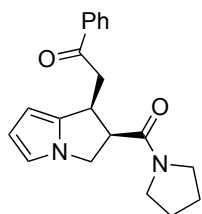




29

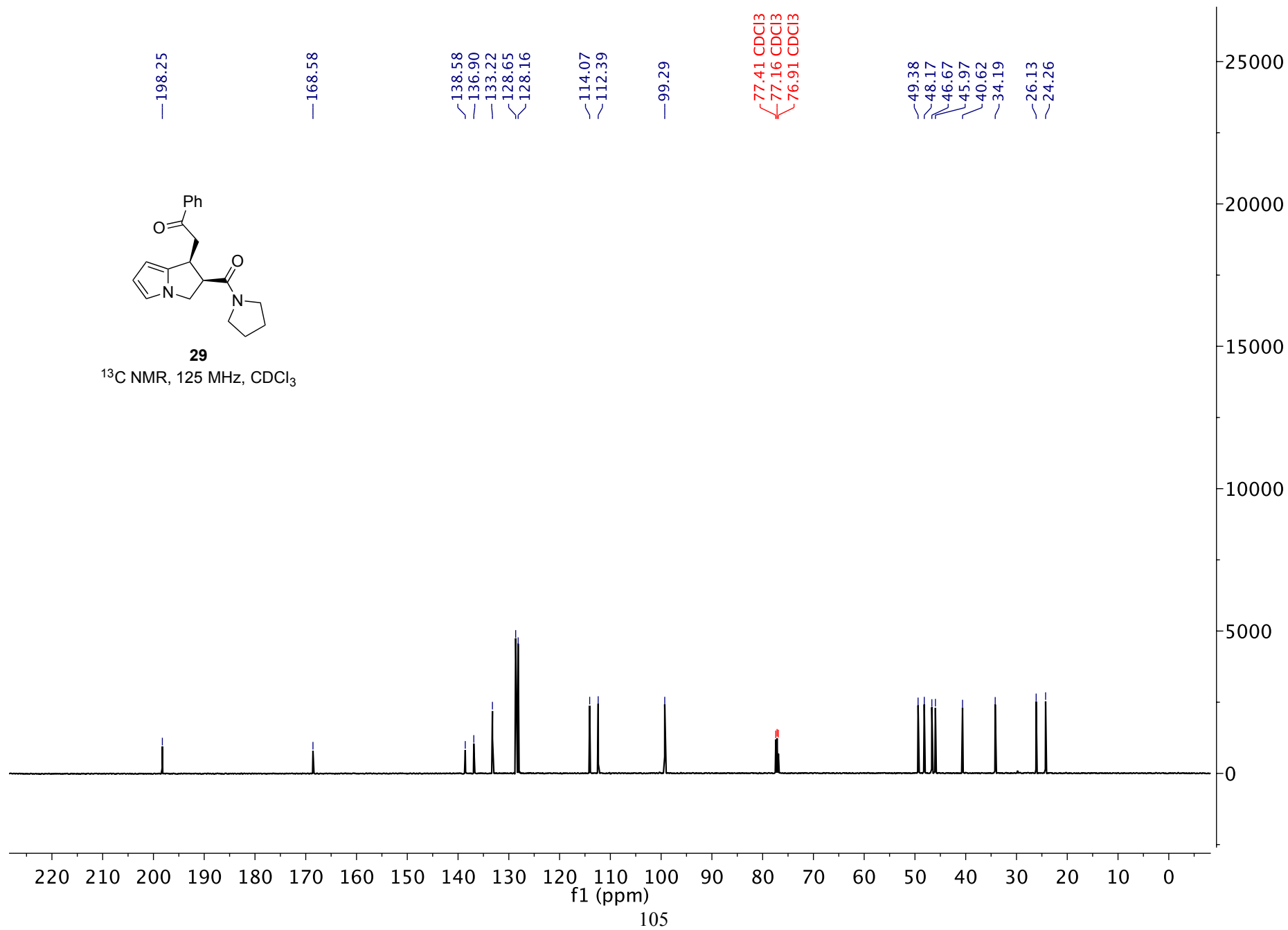
¹H NMR, 500 MHz, CDCl₃

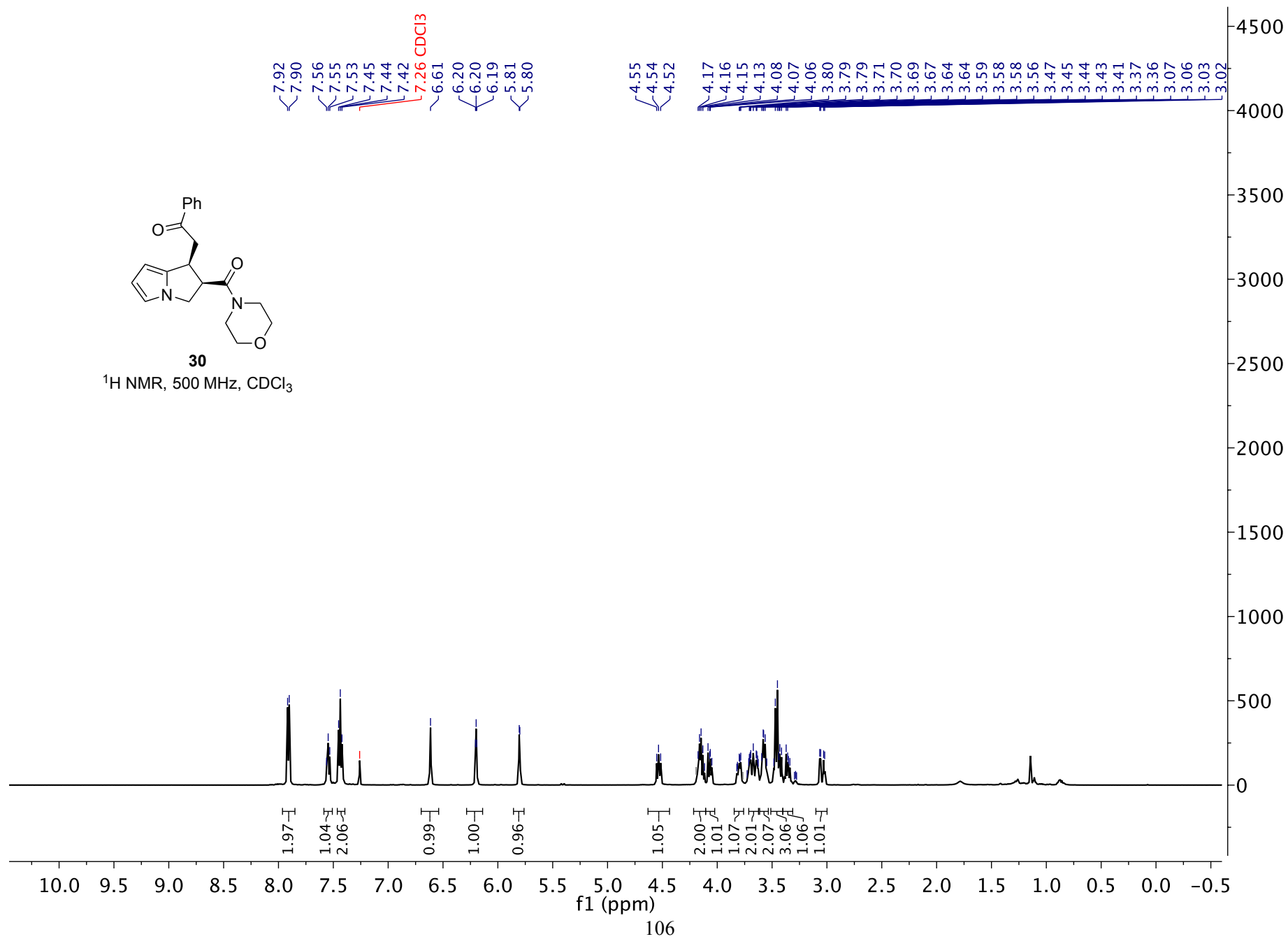
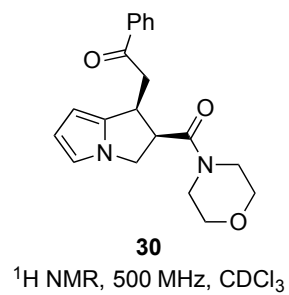


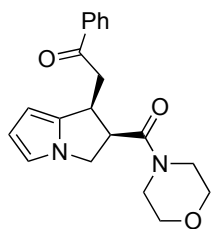


29

^{13}C NMR, 125 MHz, CDCl_3

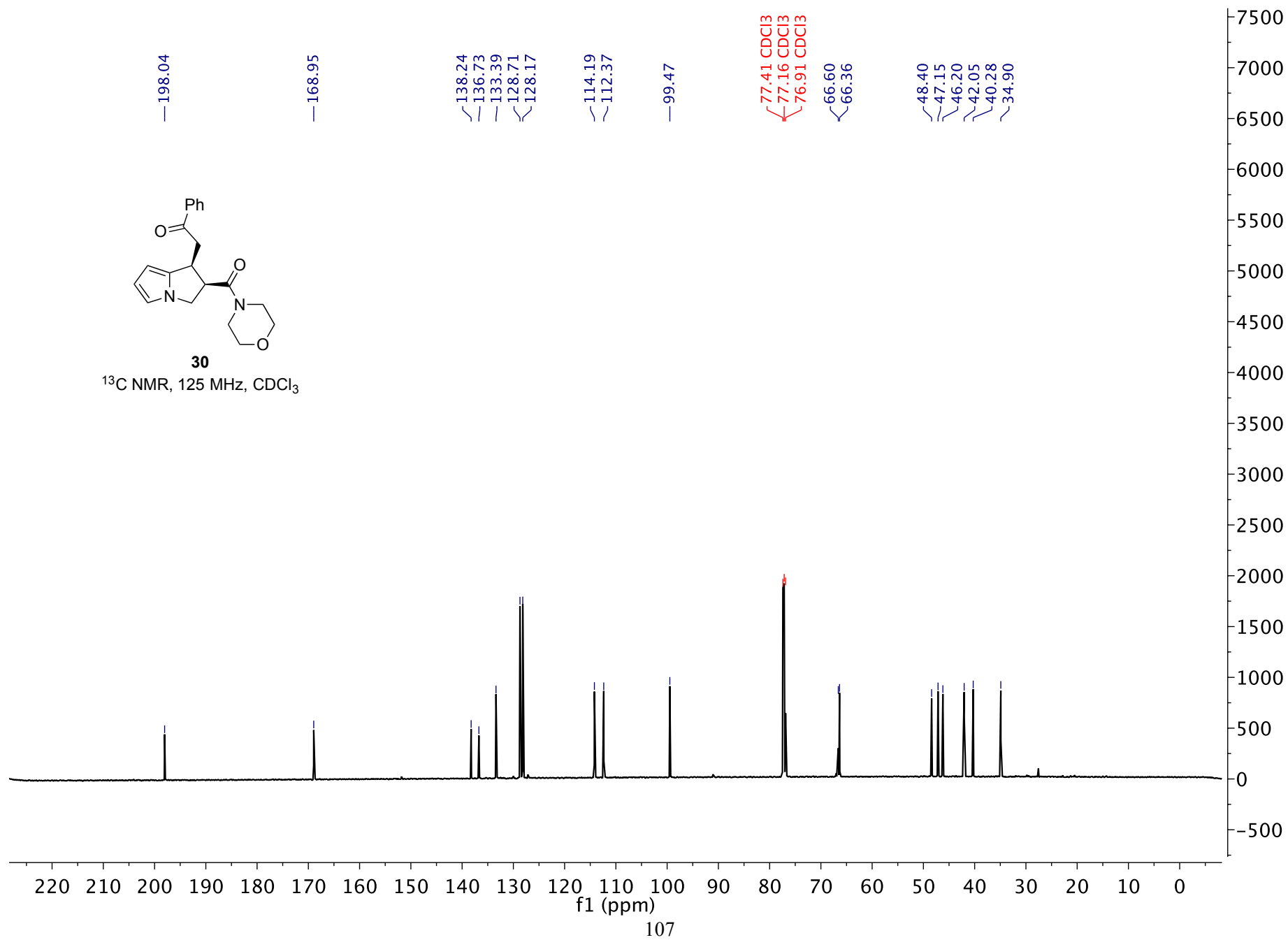


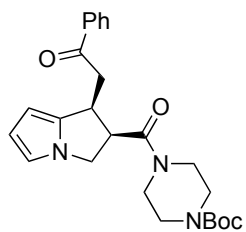




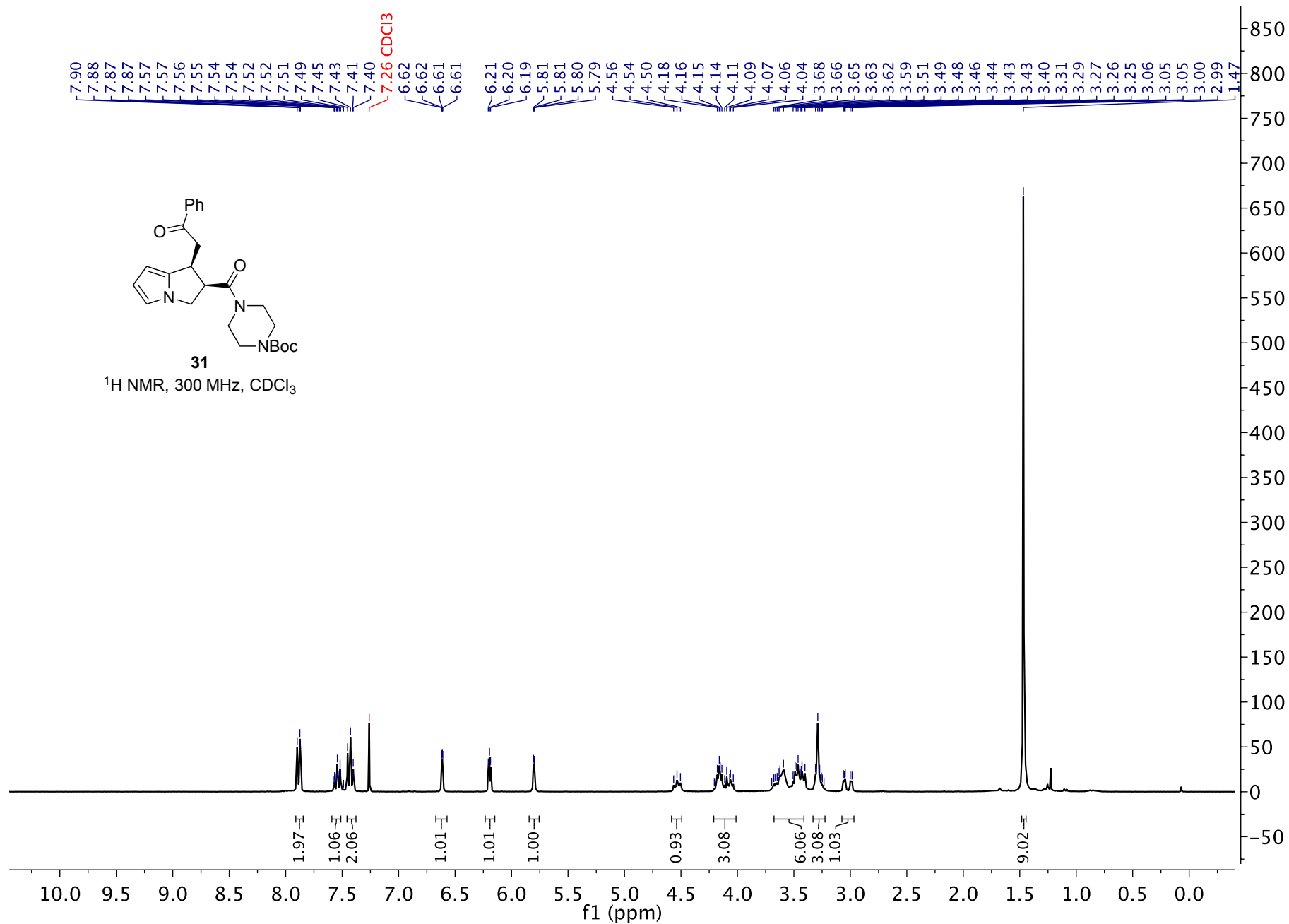
30

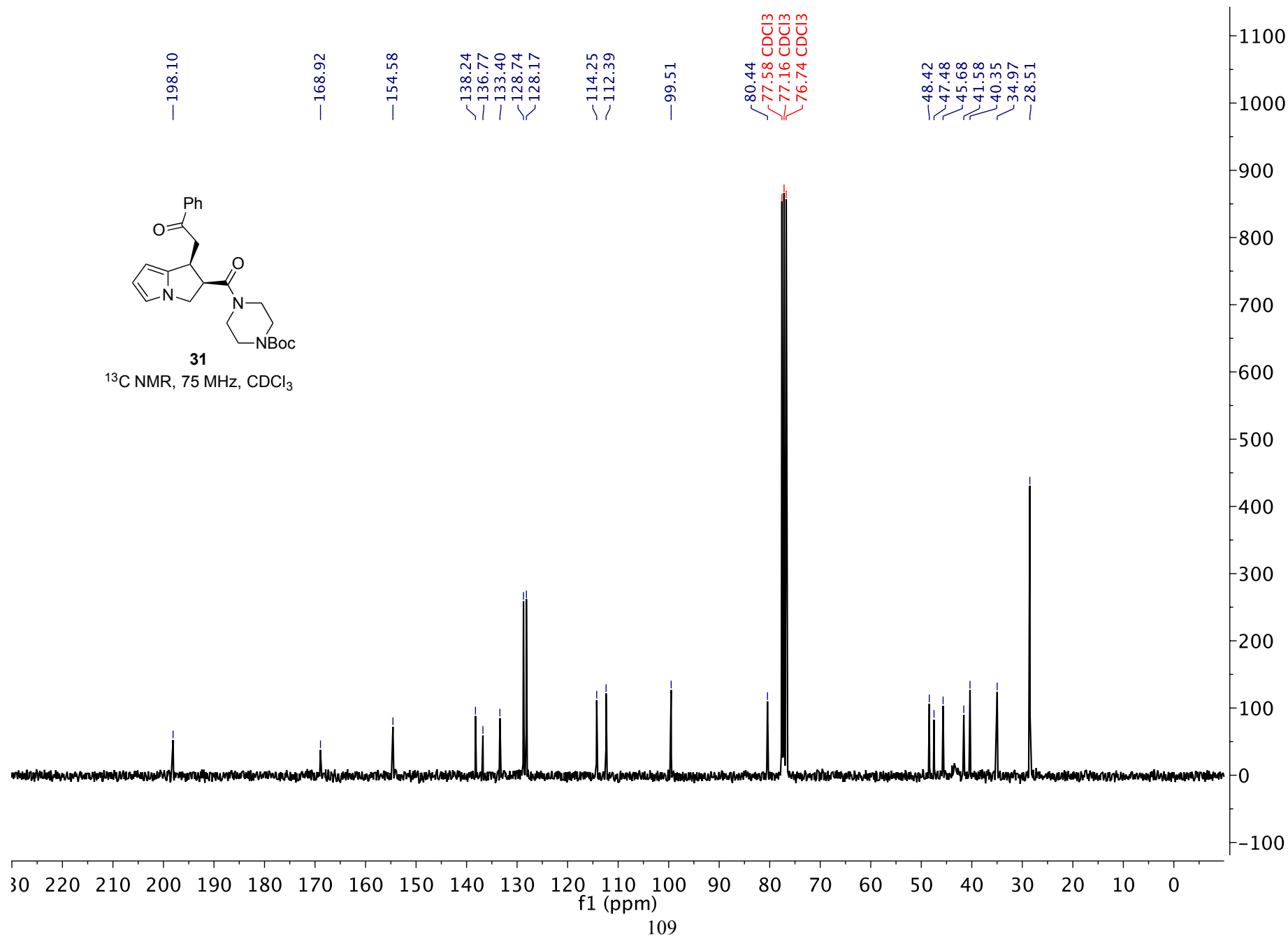
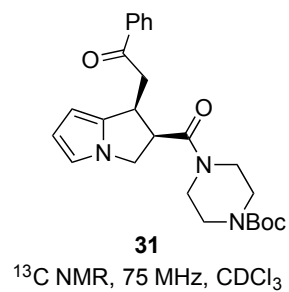
^{13}C NMR, 125 MHz, CDCl_3

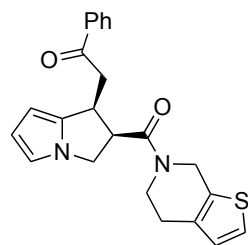




¹H NMR, 300 MHz, CDCl₃

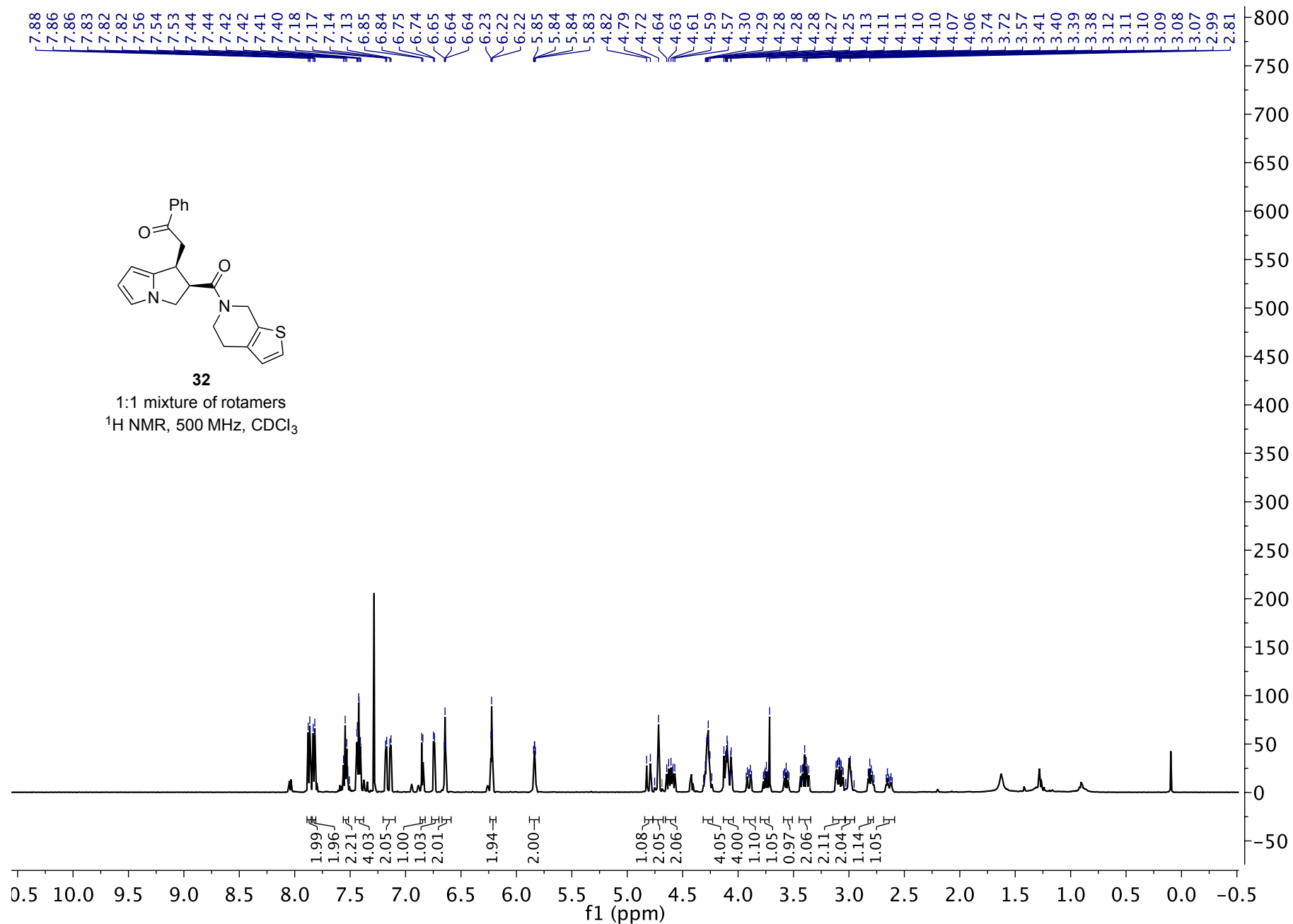


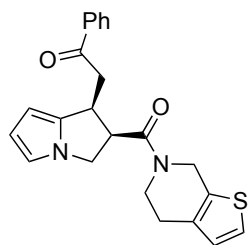




32

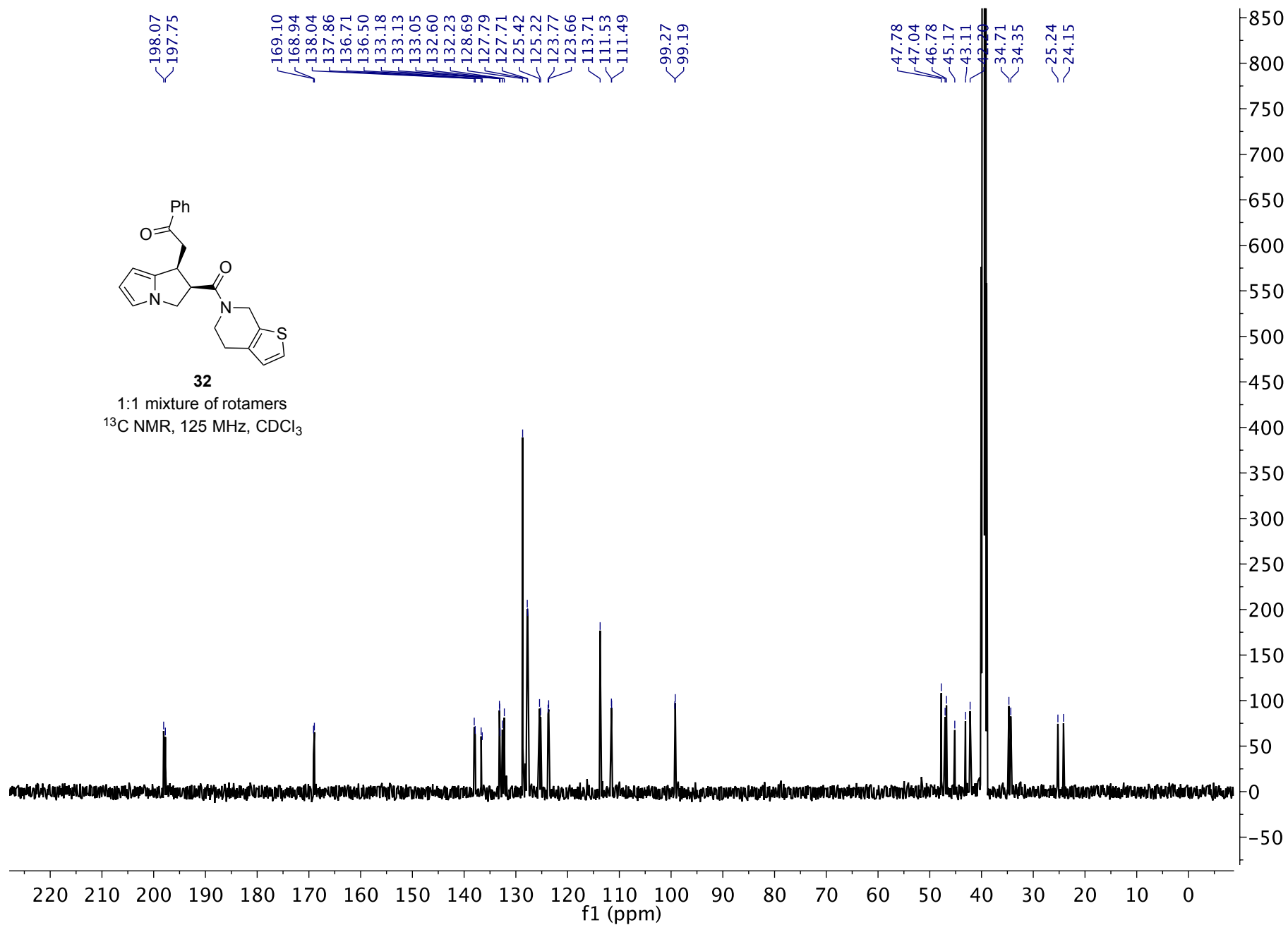
1:1 mixture of rotamers
¹H NMR, 500 MHz, CDCl₃

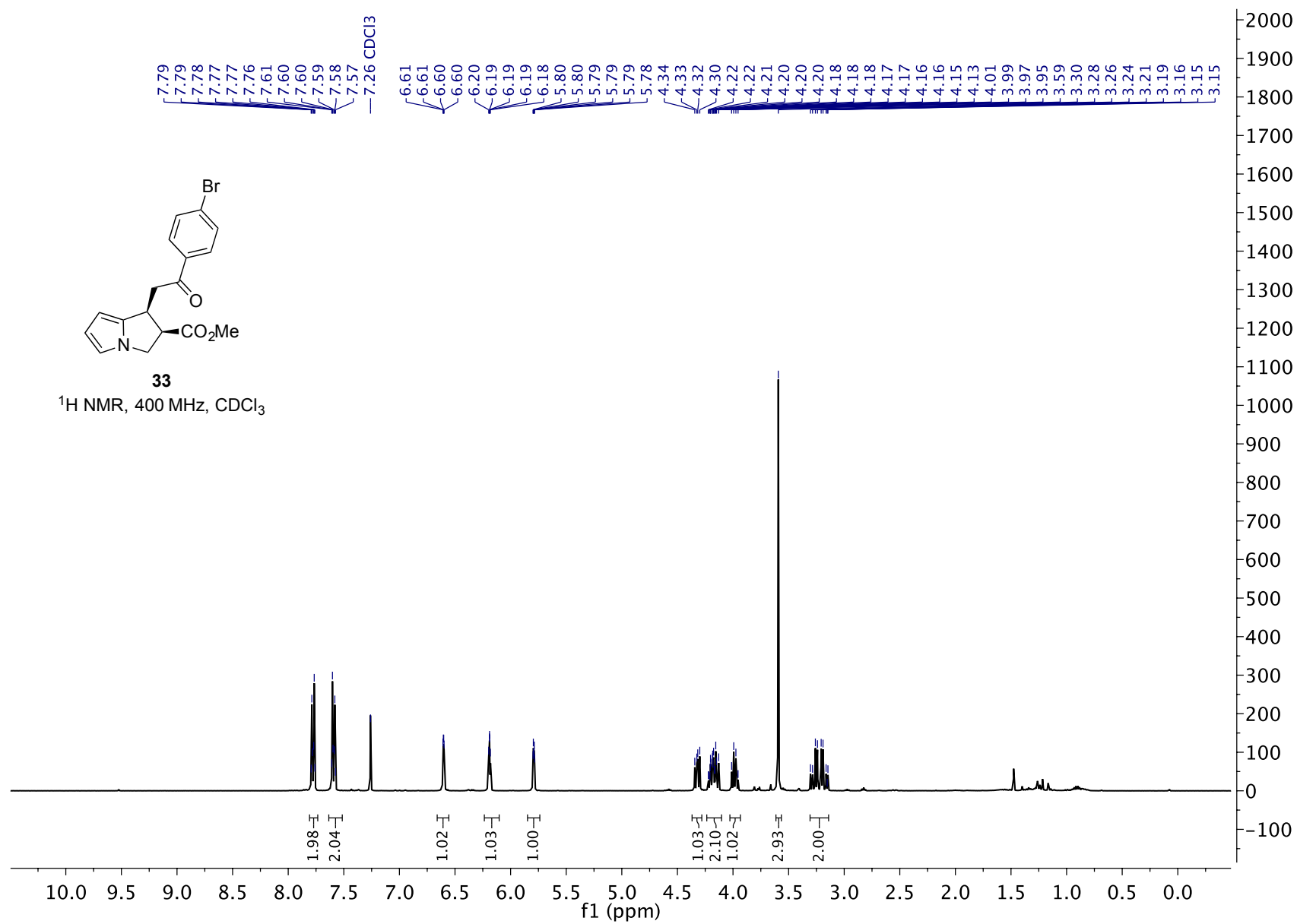


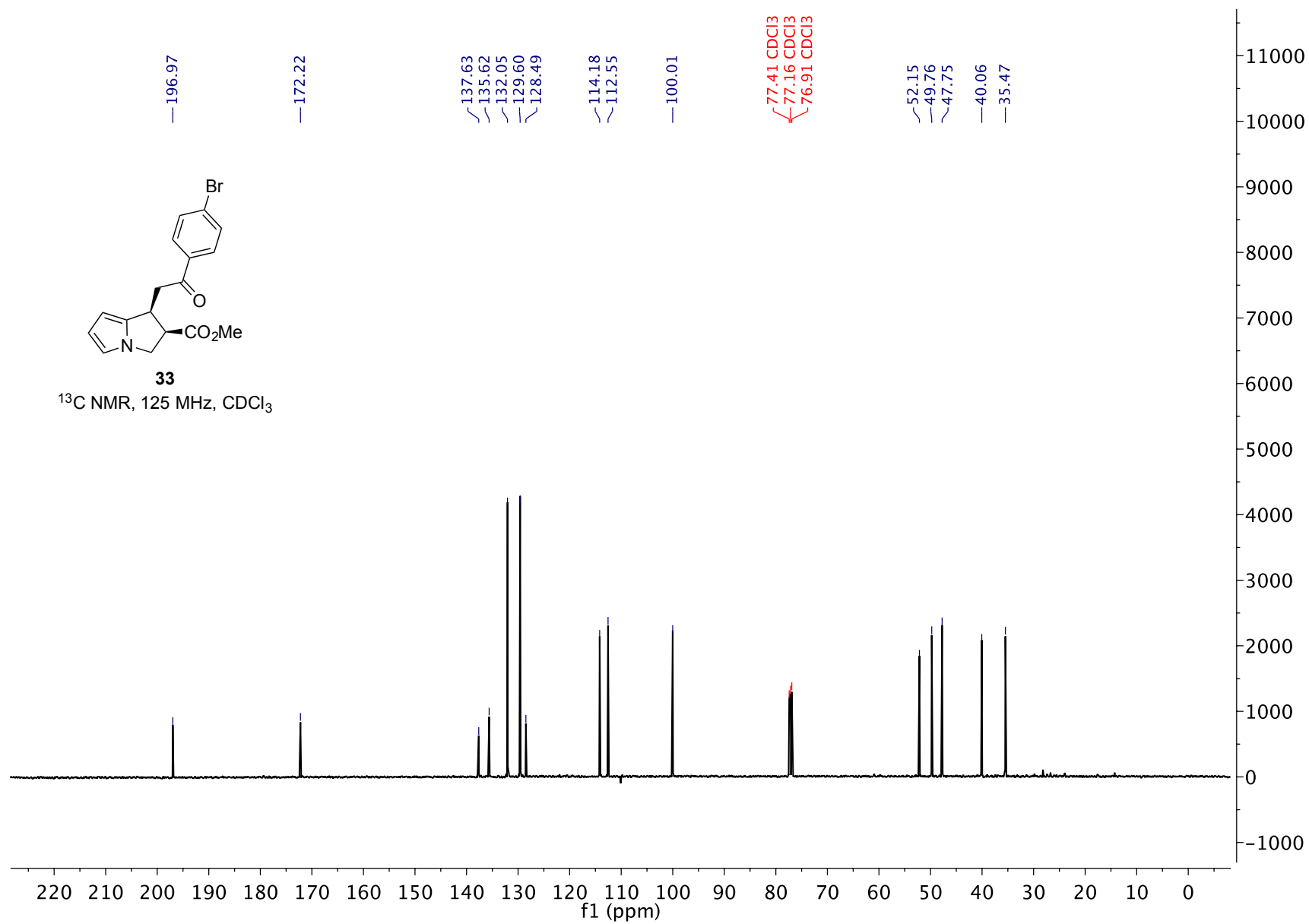


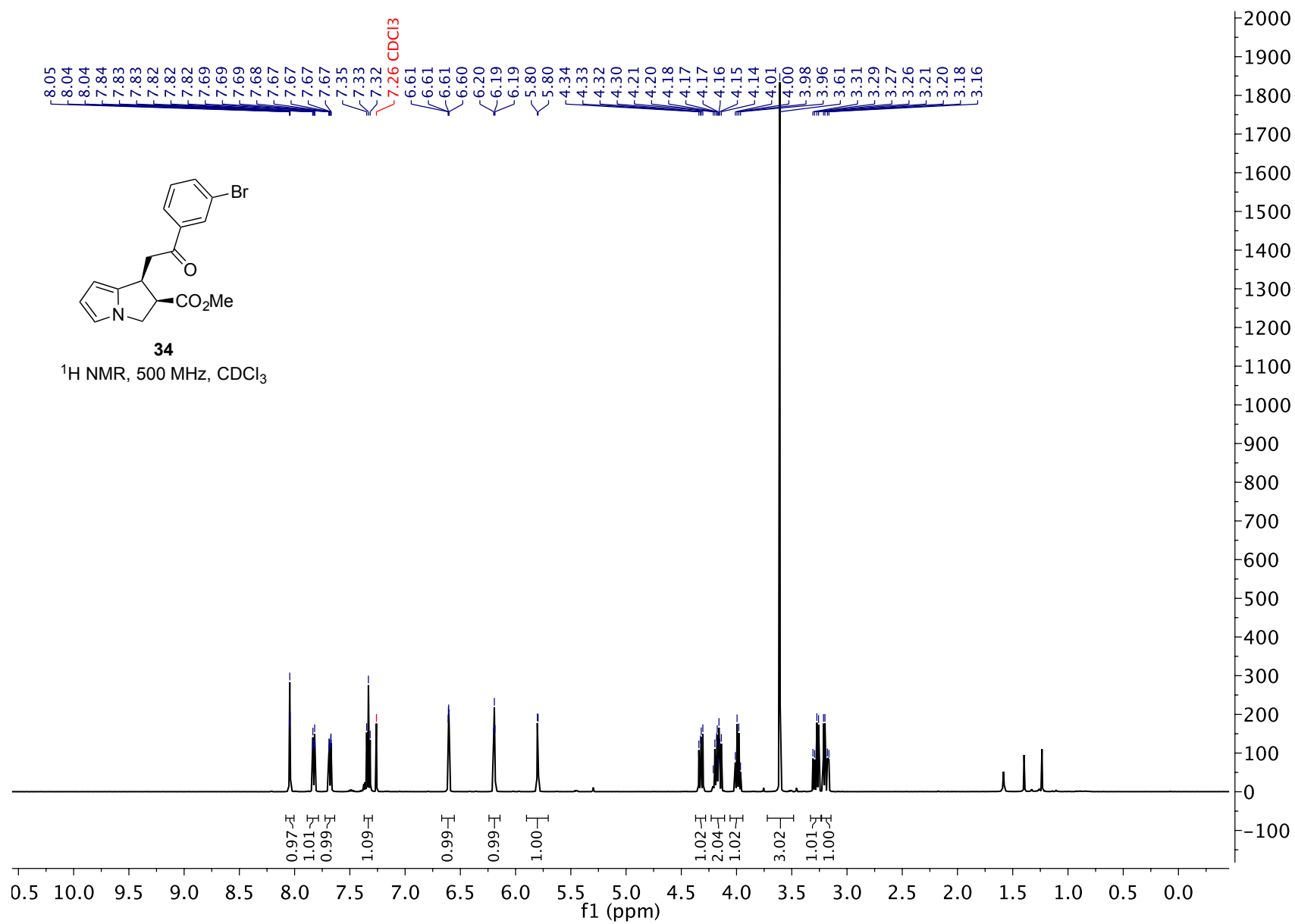
32

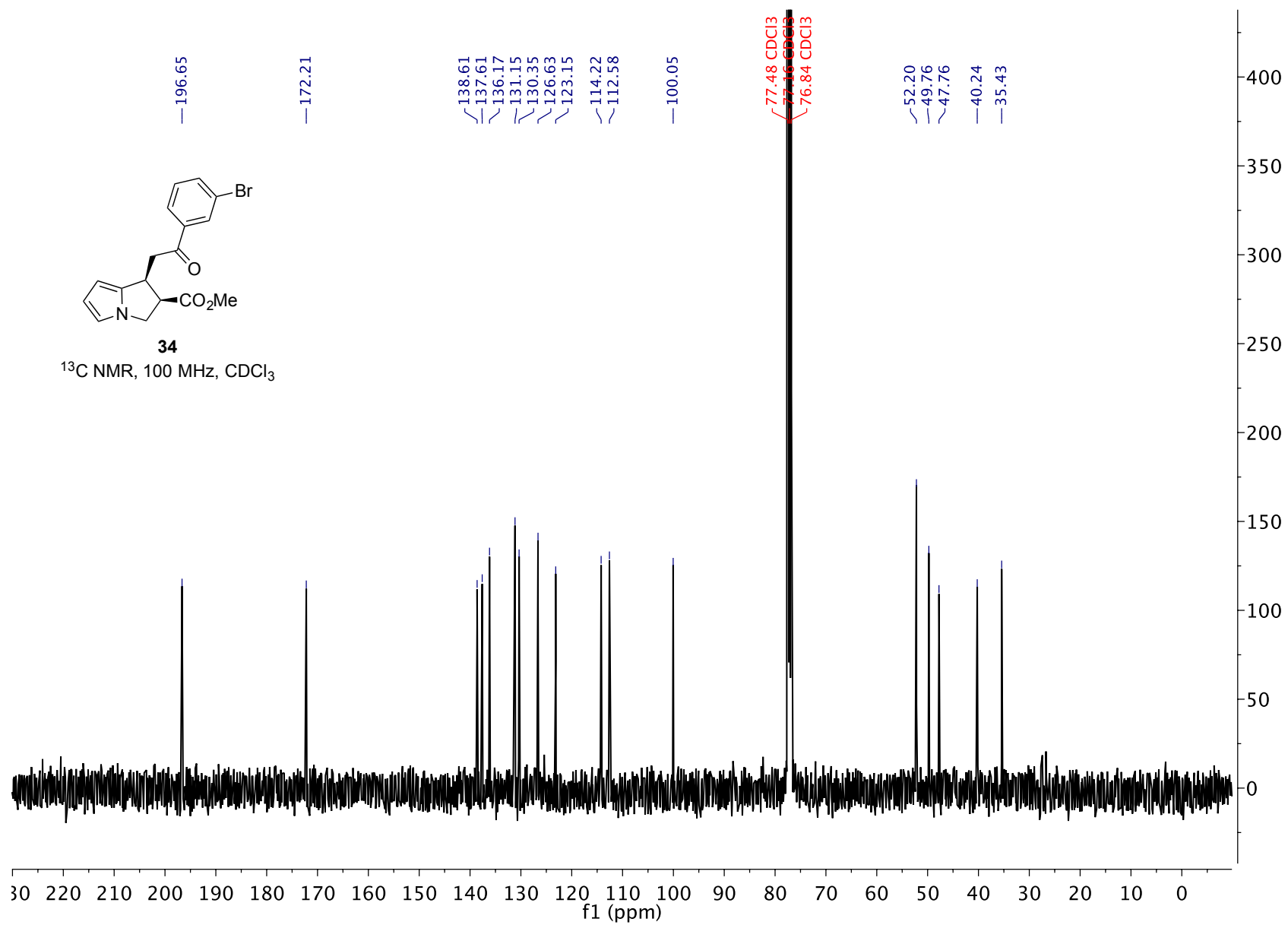
1:1 mixture of rotamers
 ^{13}C NMR, 125 MHz, CDCl_3

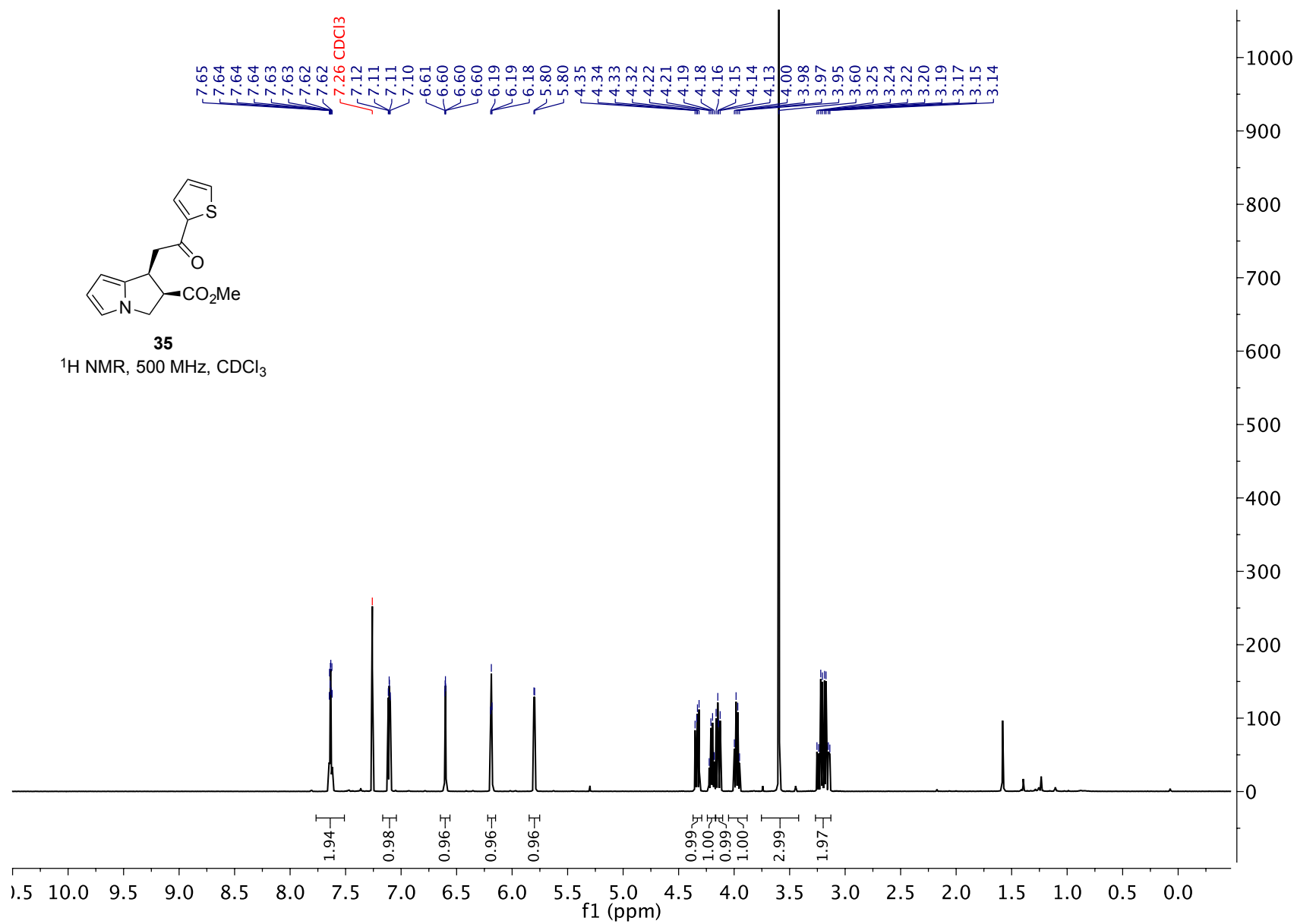


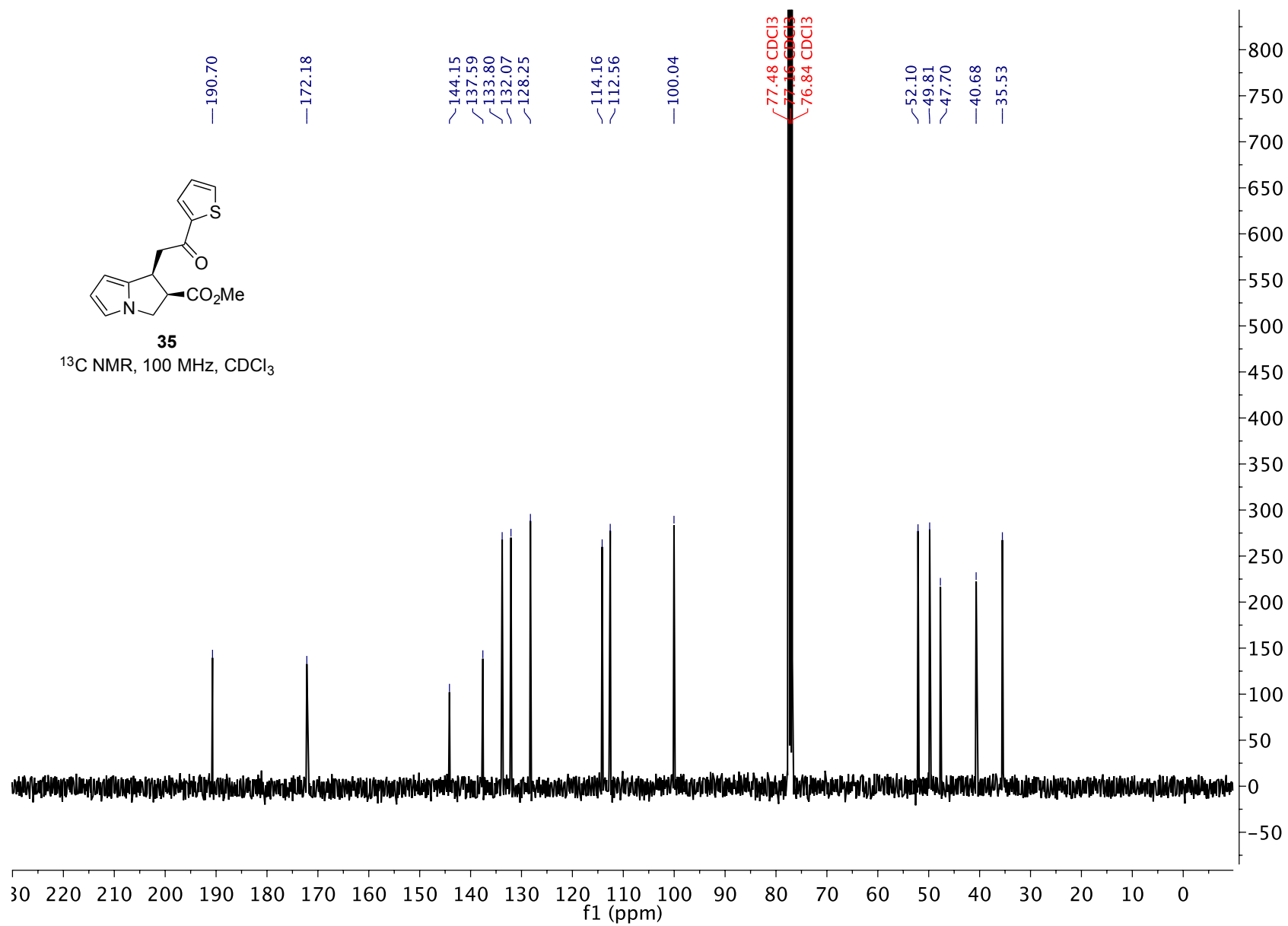


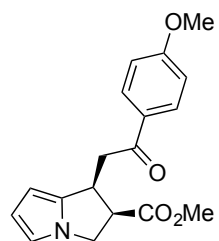






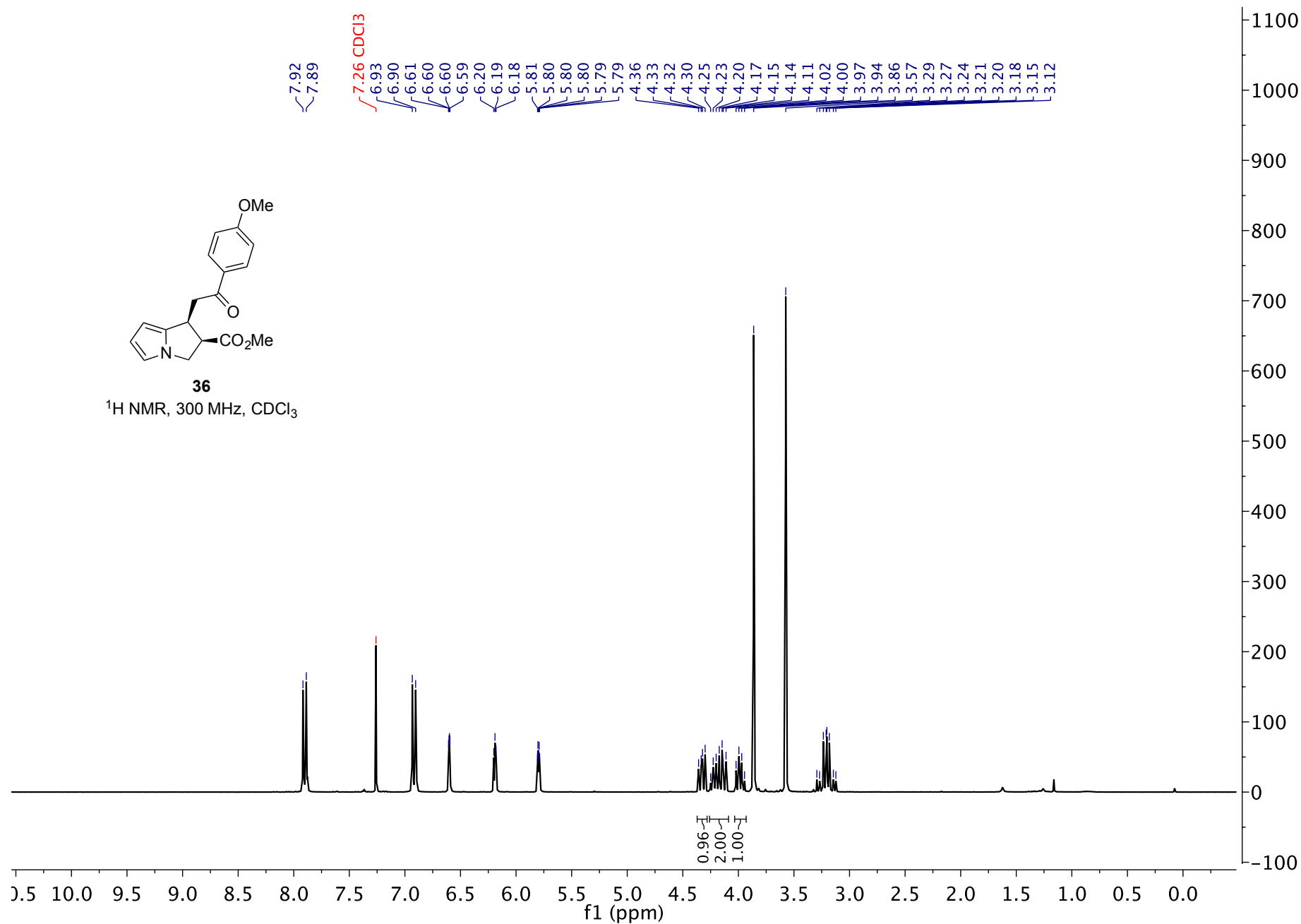


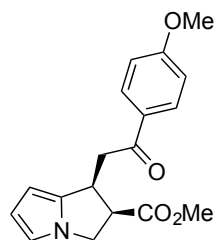




36

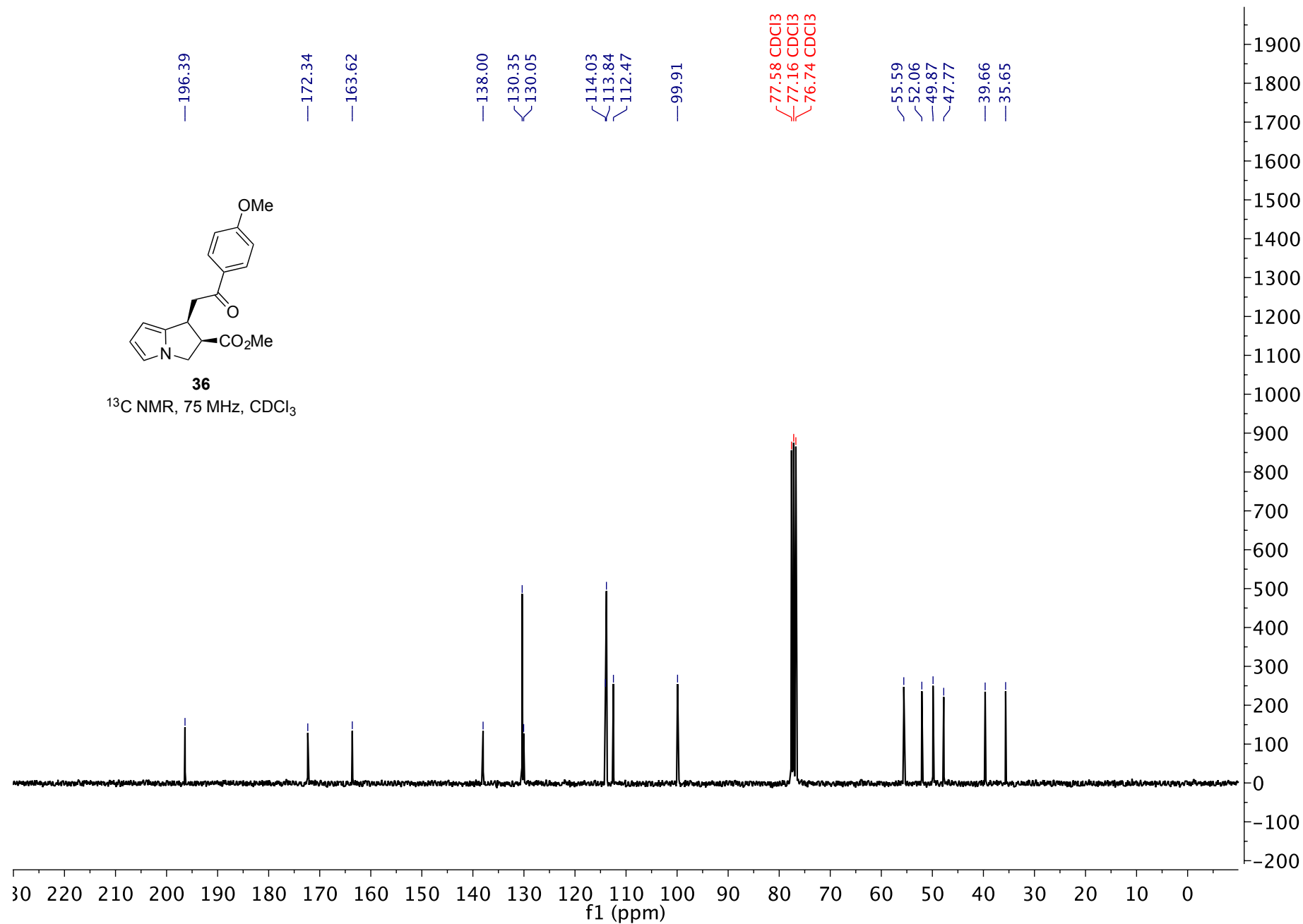
¹H NMR, 300 MHz, CDCl₃

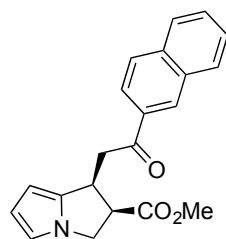




36

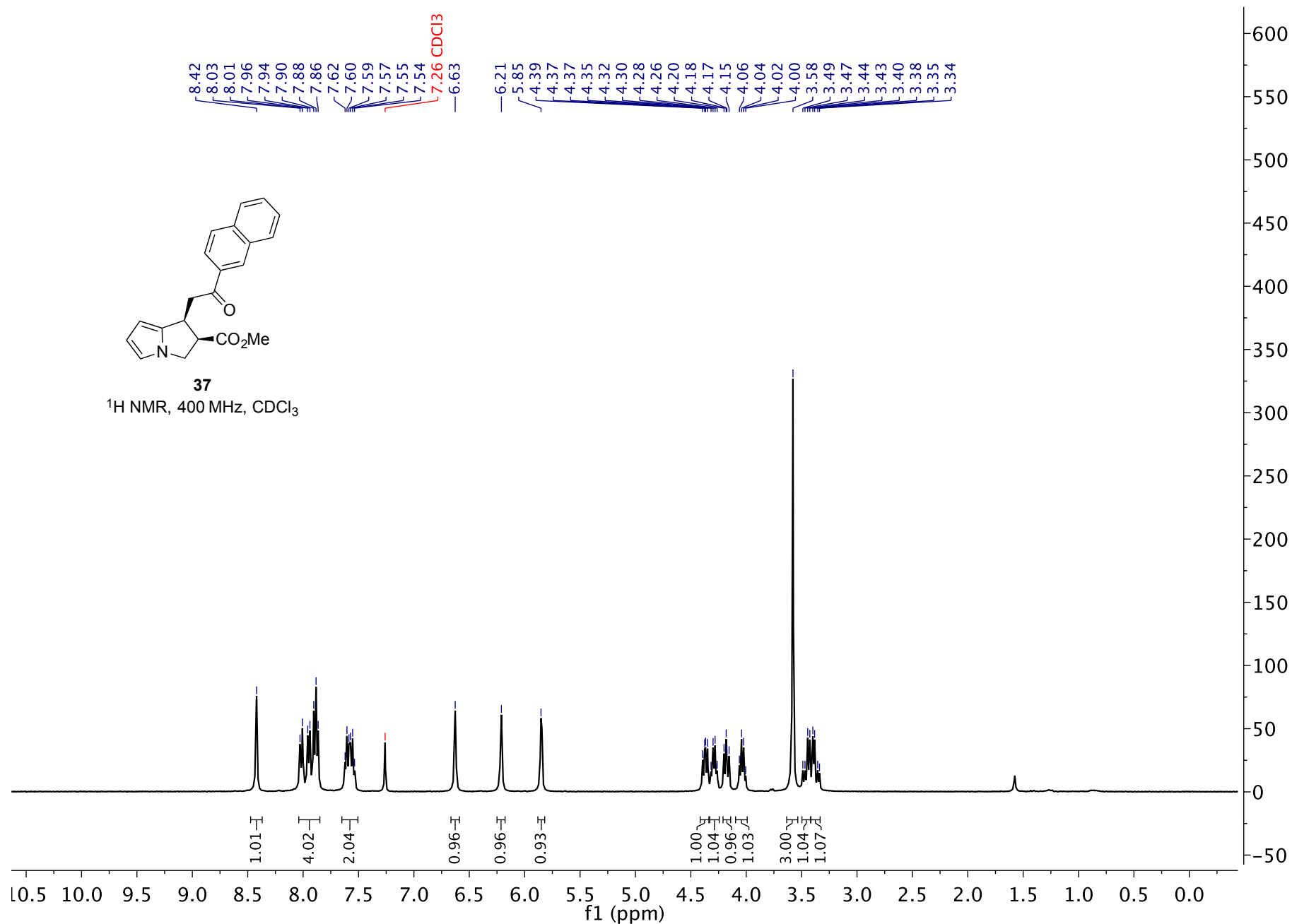
^{13}C NMR, 75 MHz, CDCl_3

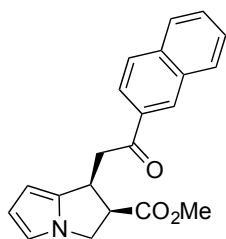




37

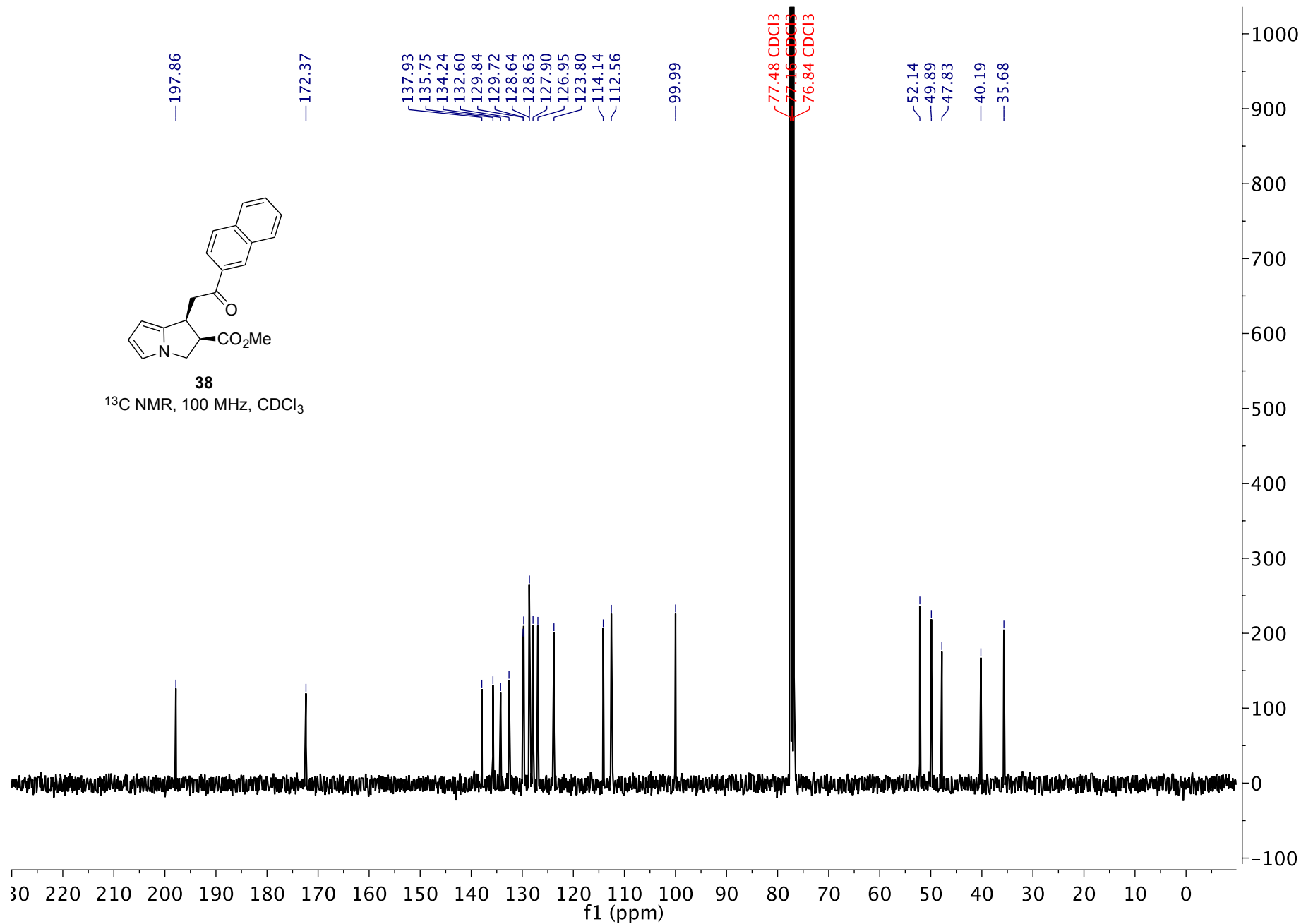
¹H NMR, 400 MHz, CDCl₃

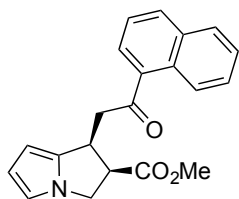




38

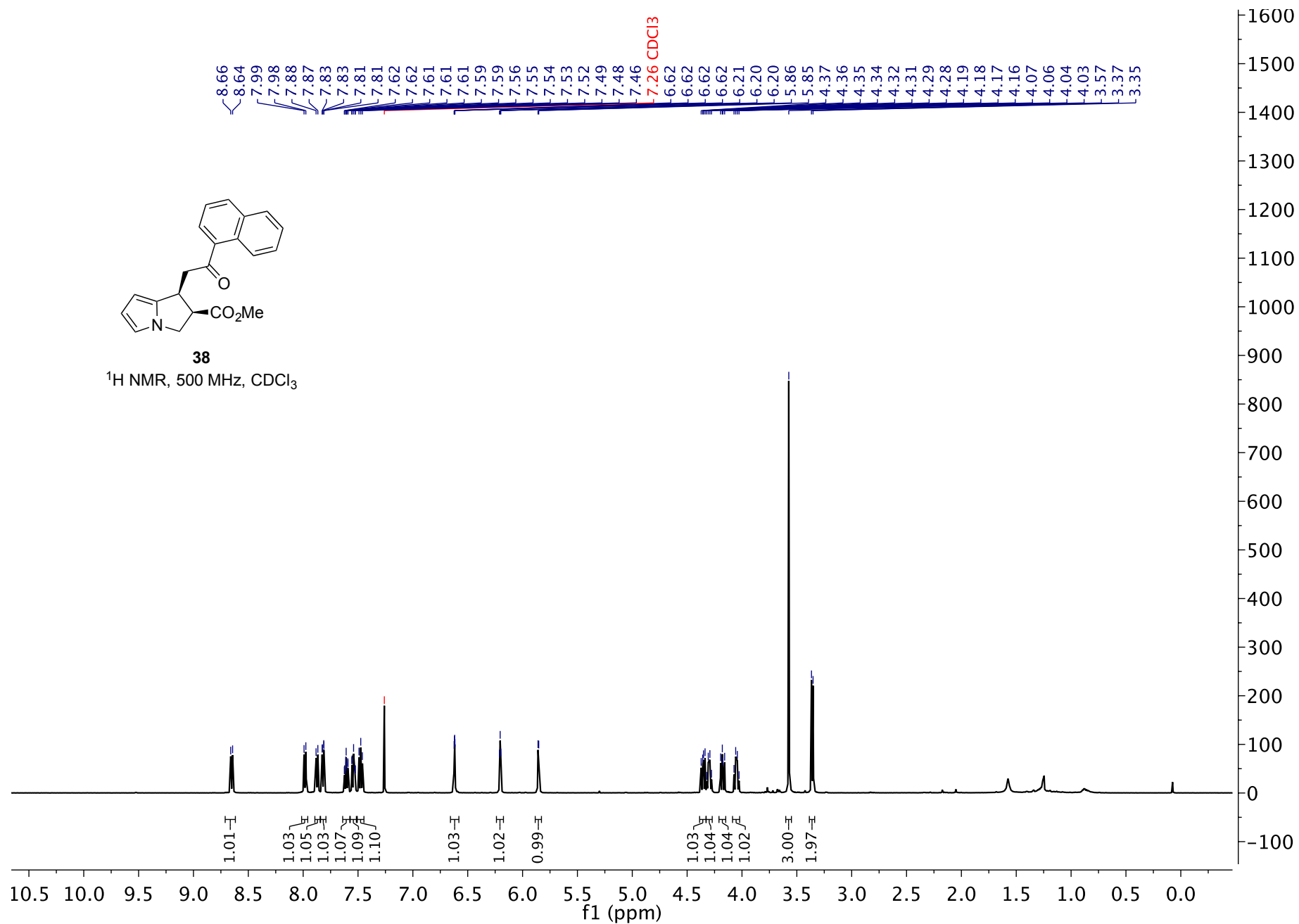
^{13}C NMR, 100 MHz, CDCl_3

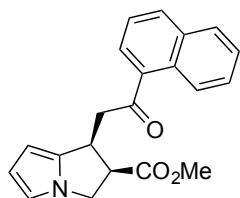




38

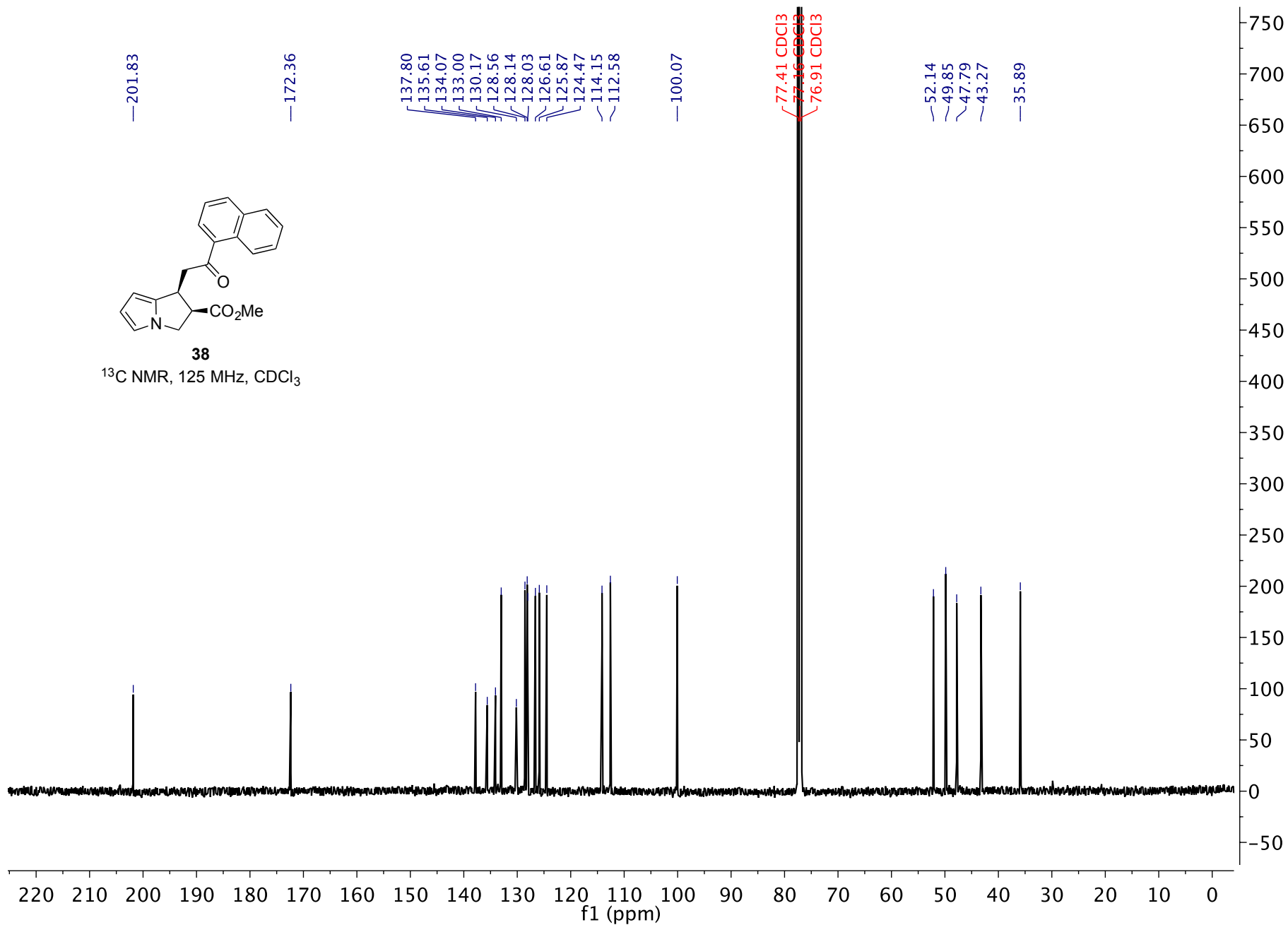
^1H NMR, 500 MHz, CDCl_3

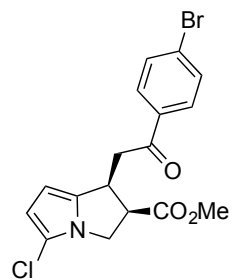




38

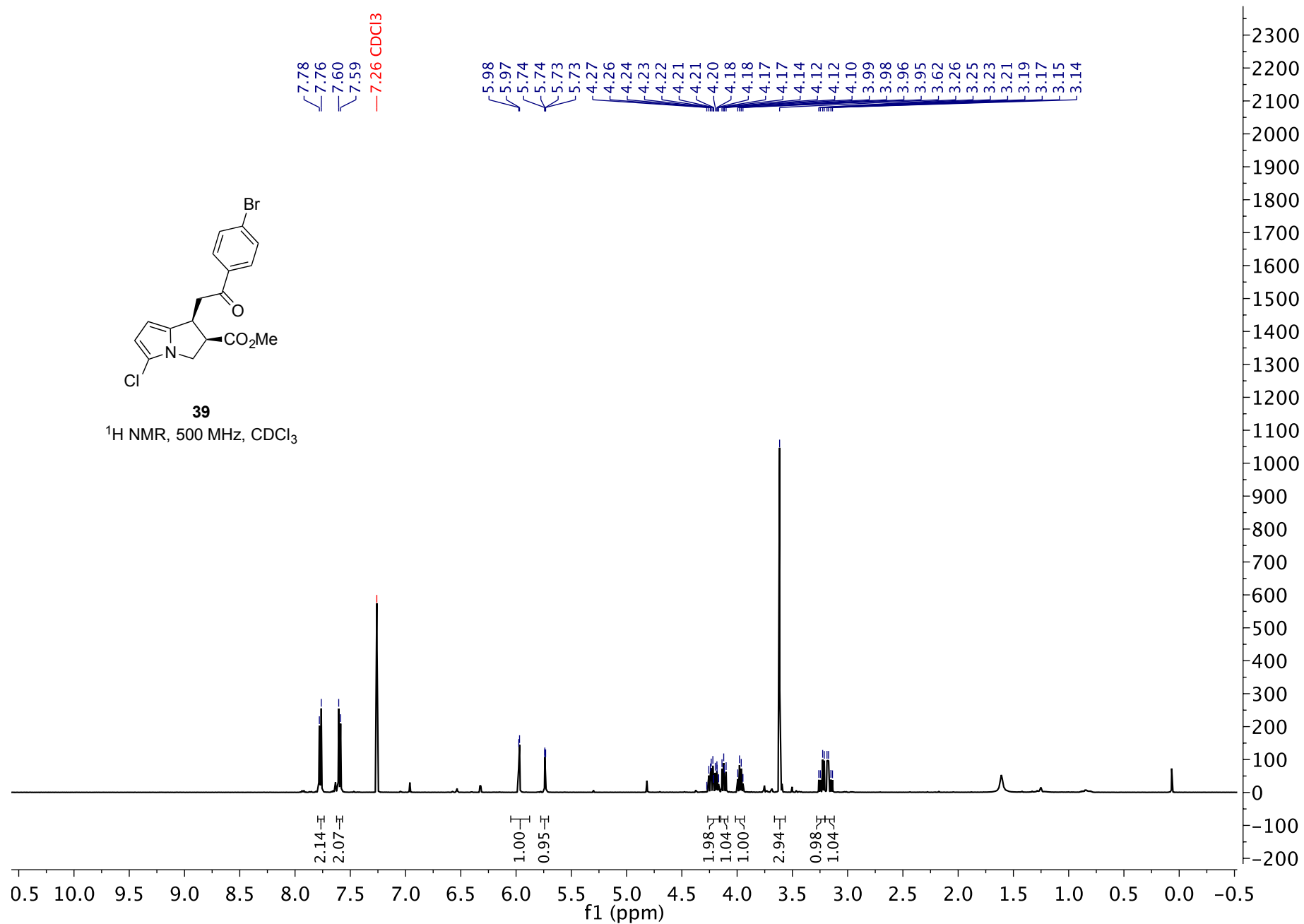
^{13}C NMR, 125 MHz, CDCl_3

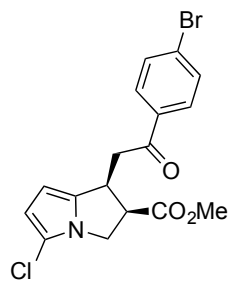




39

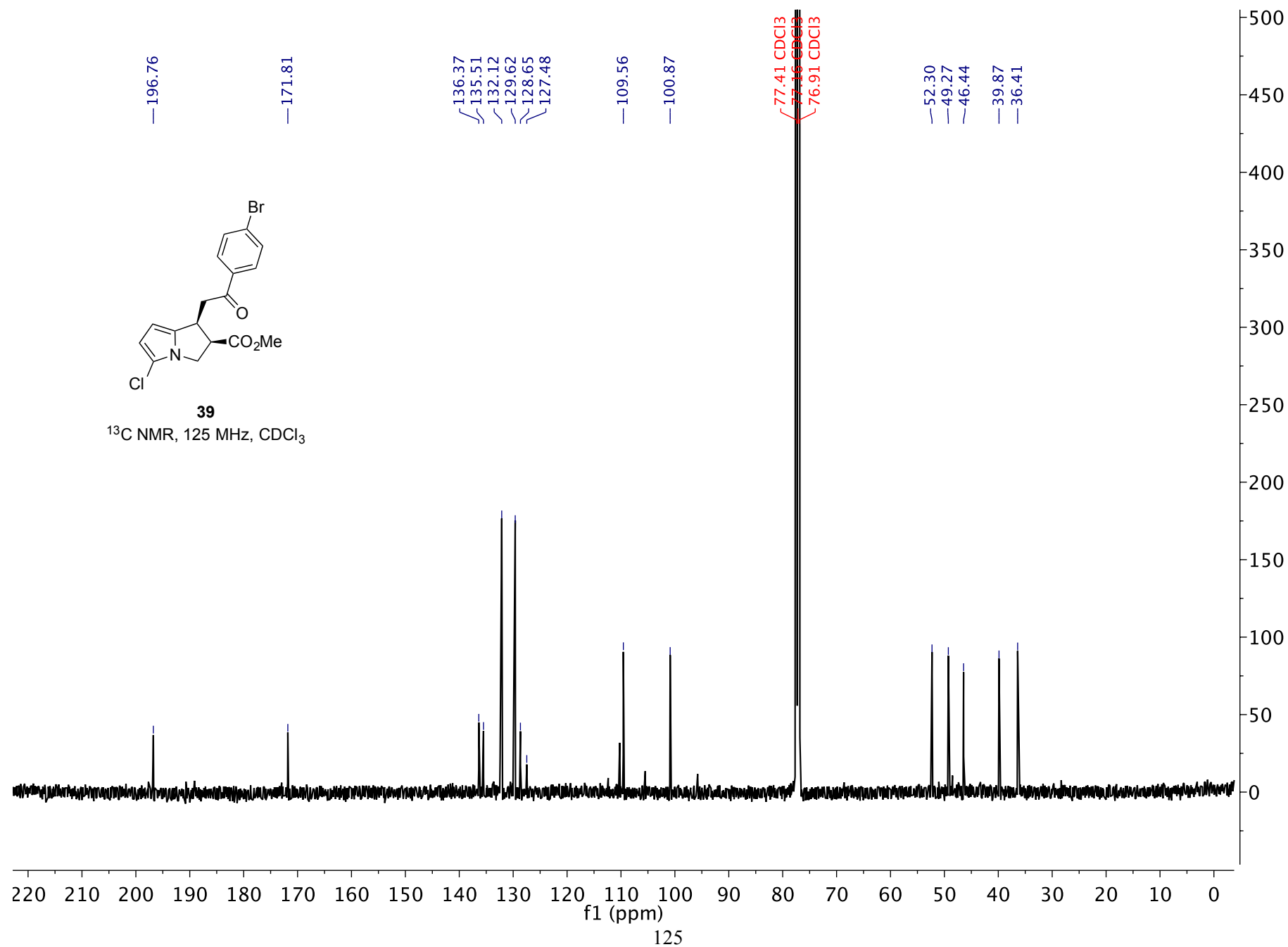
^1H NMR, 500 MHz, CDCl_3

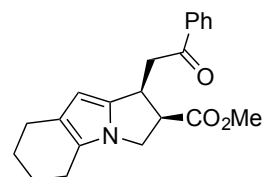




39

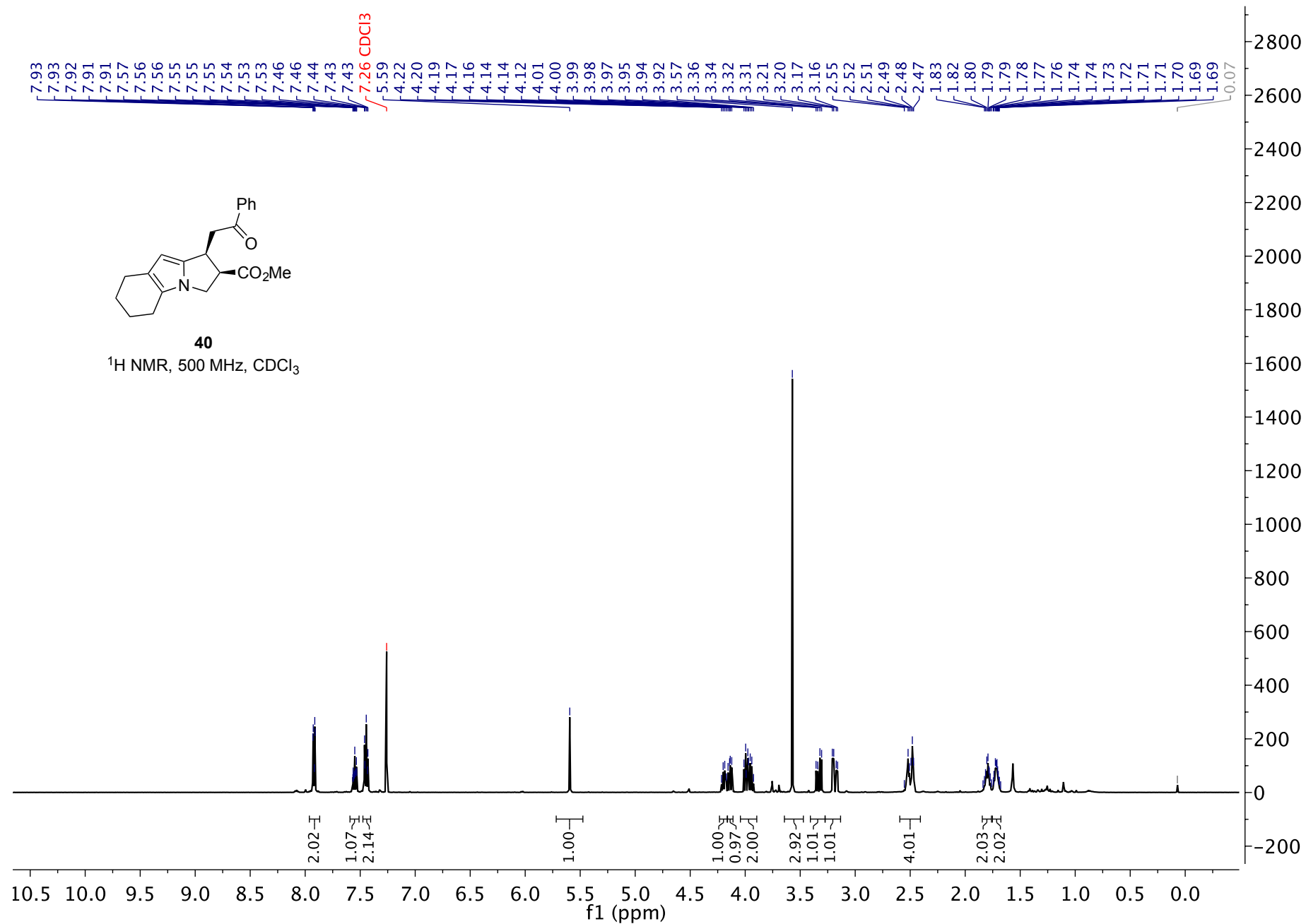
^{13}C NMR, 125 MHz, CDCl_3

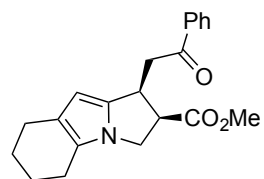




40

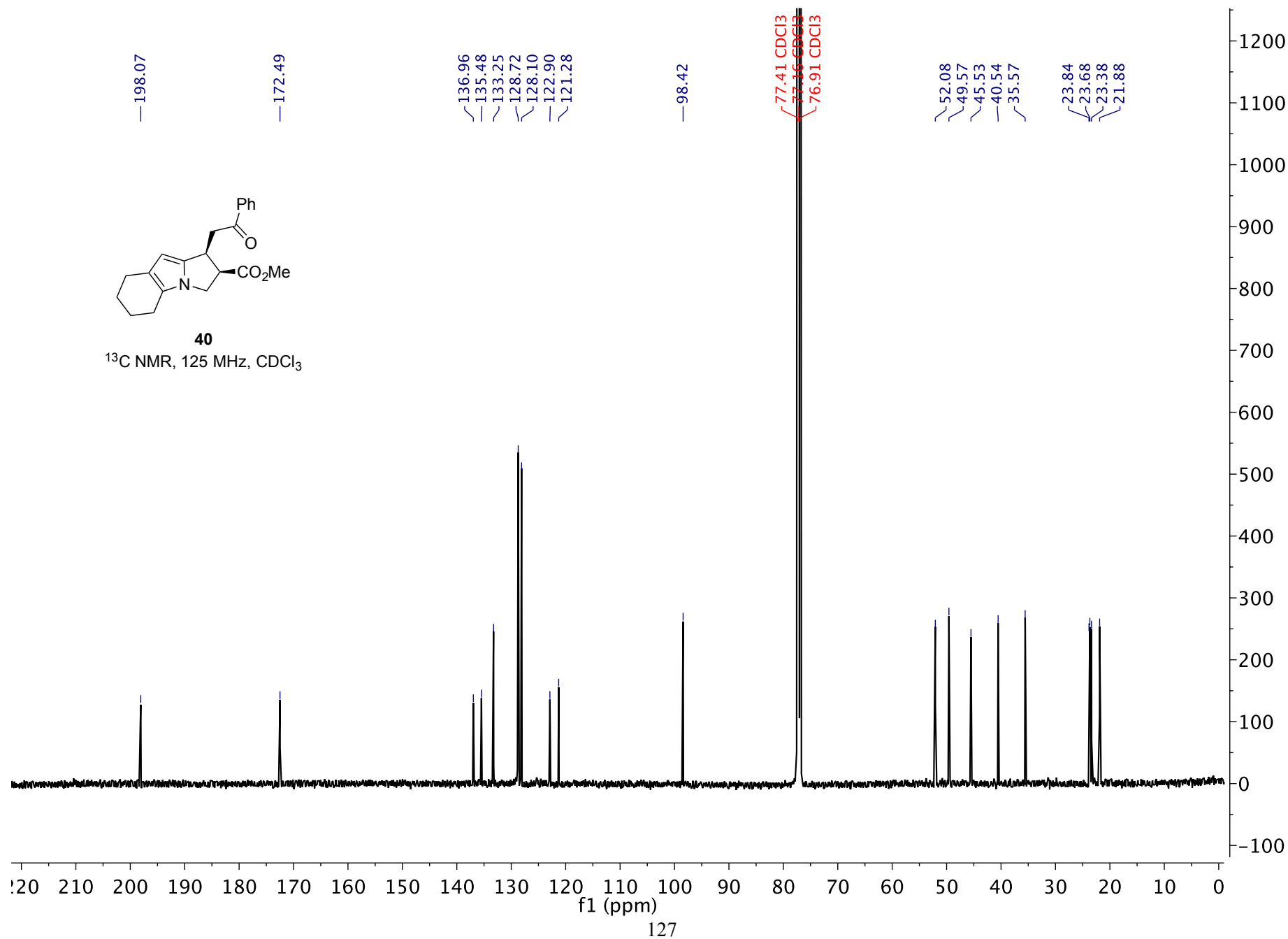
^1H NMR, 500 MHz, CDCl_3

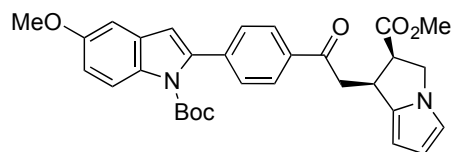




40

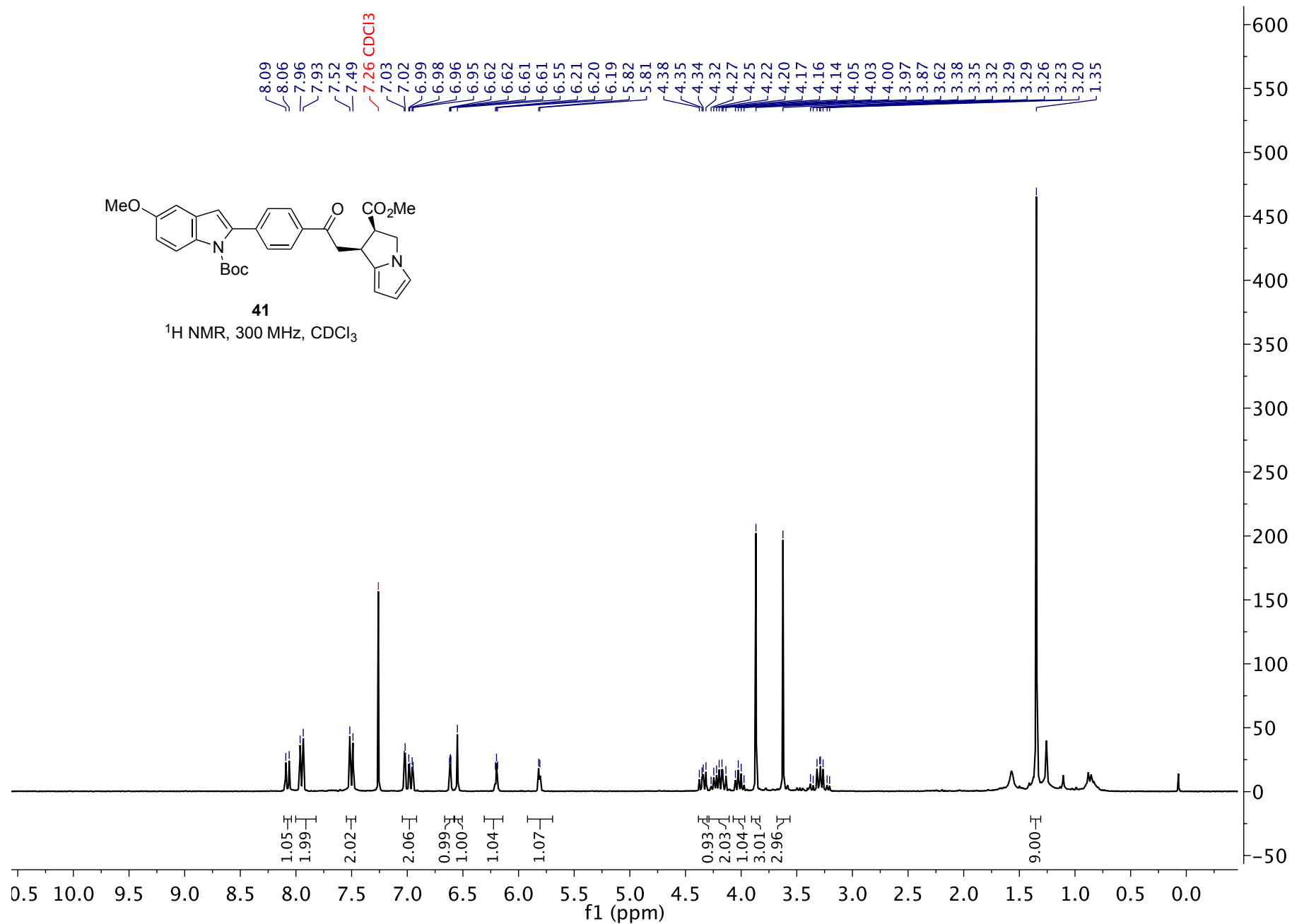
^{13}C NMR, 125 MHz, CDCl_3

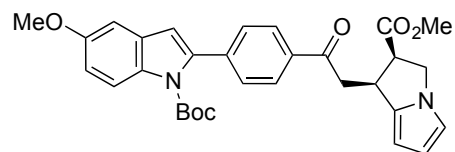




41

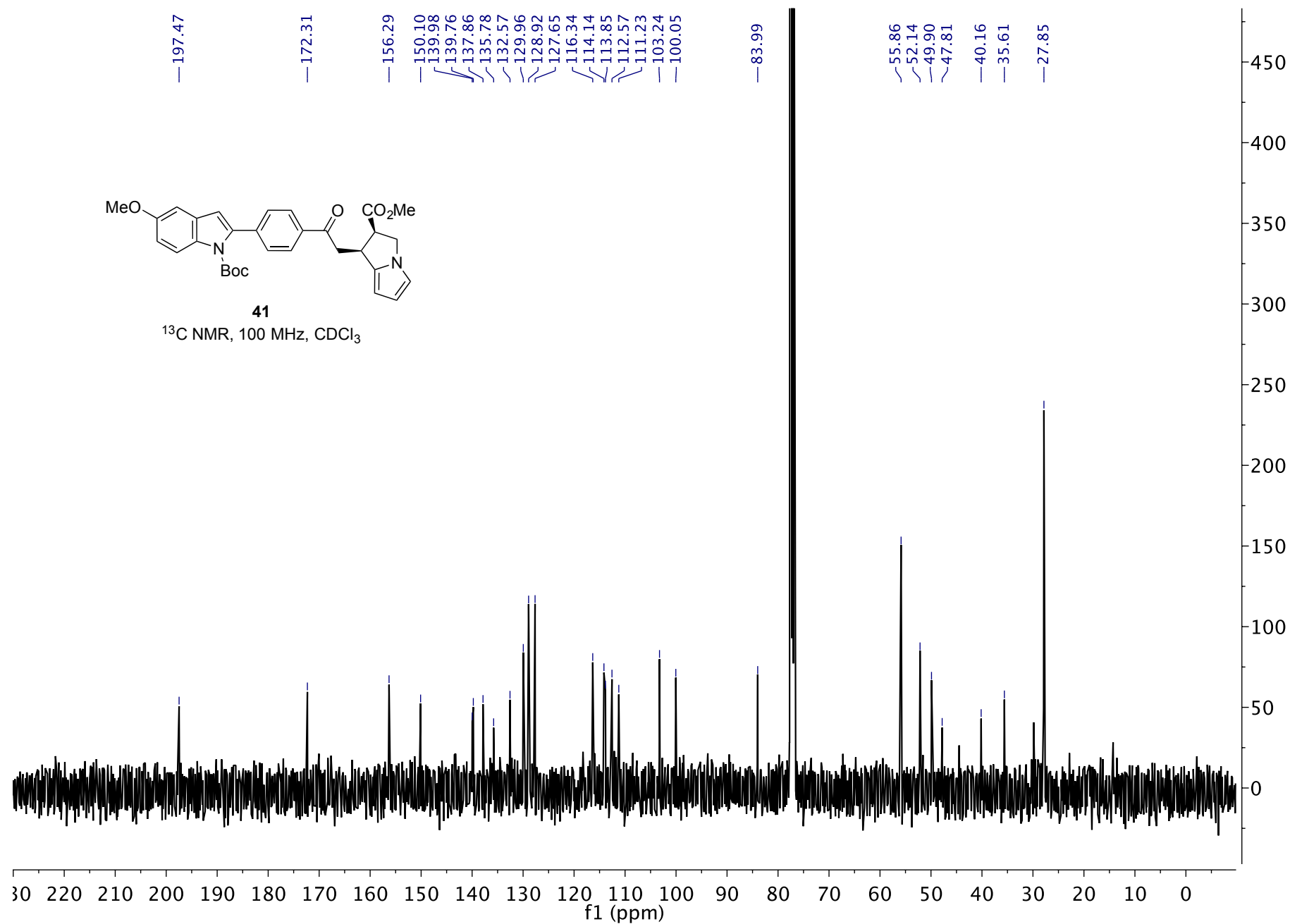
^1H NMR, 300 MHz, CDCl_3

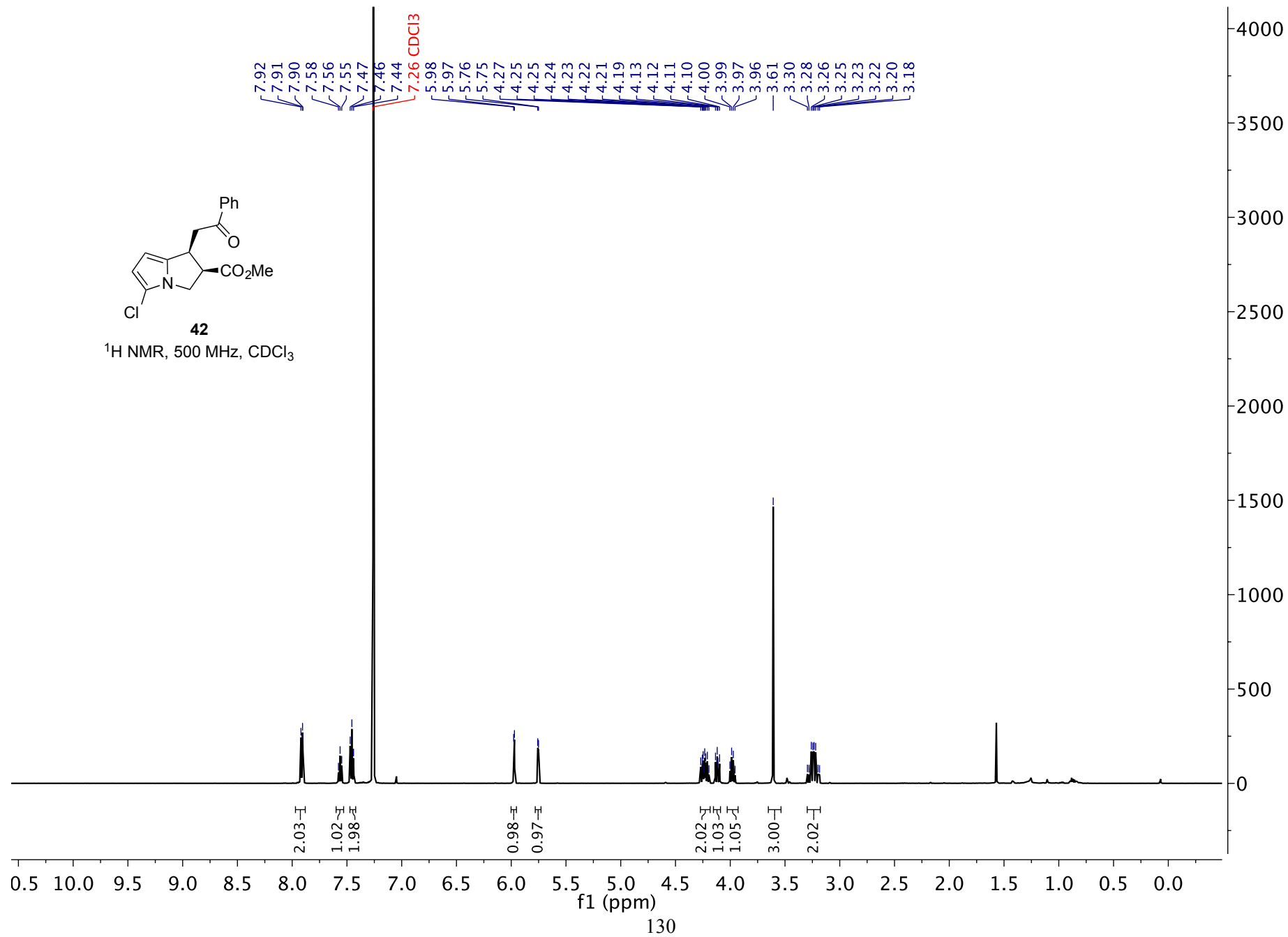
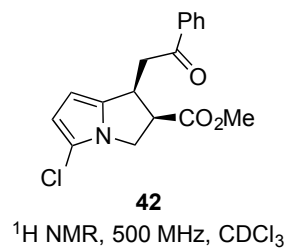


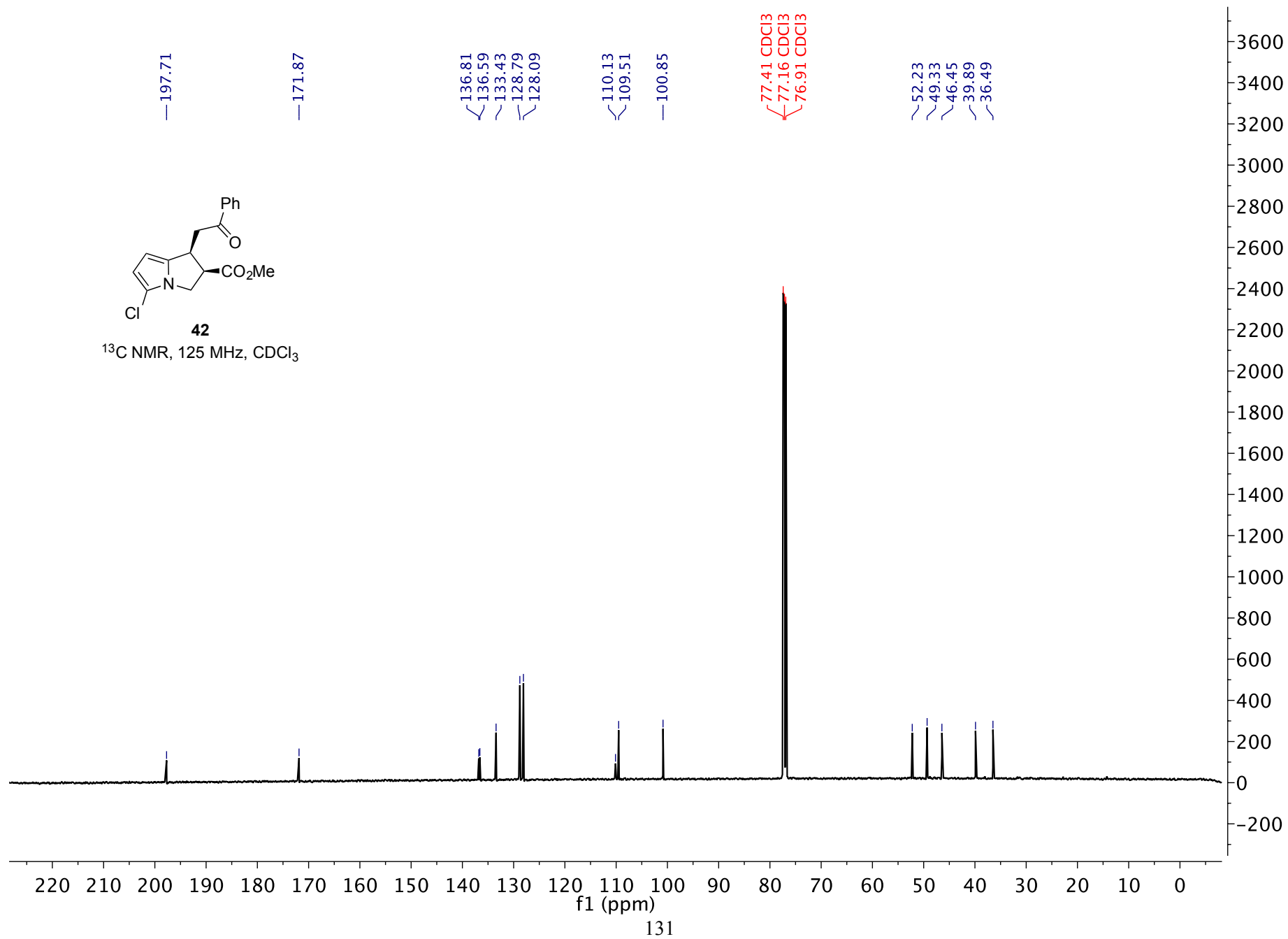
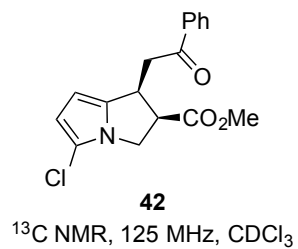


41

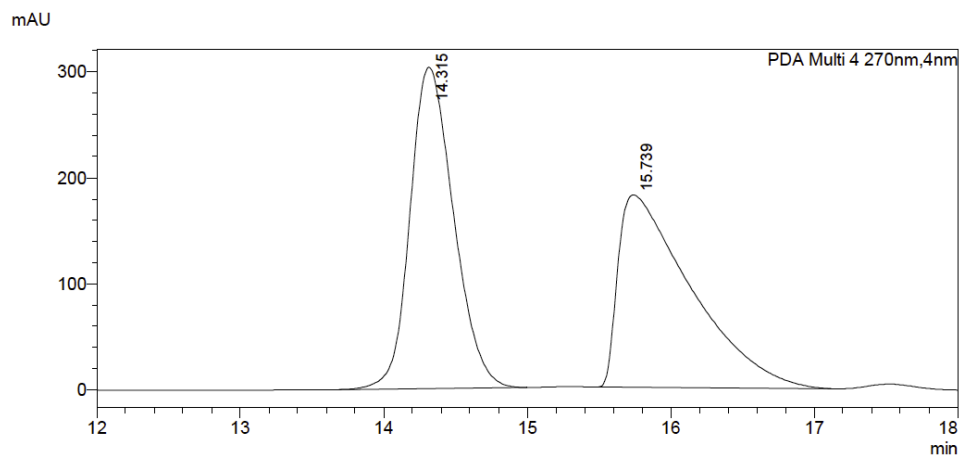
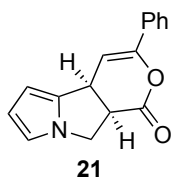
^{13}C NMR, 100 MHz, CDCl_3



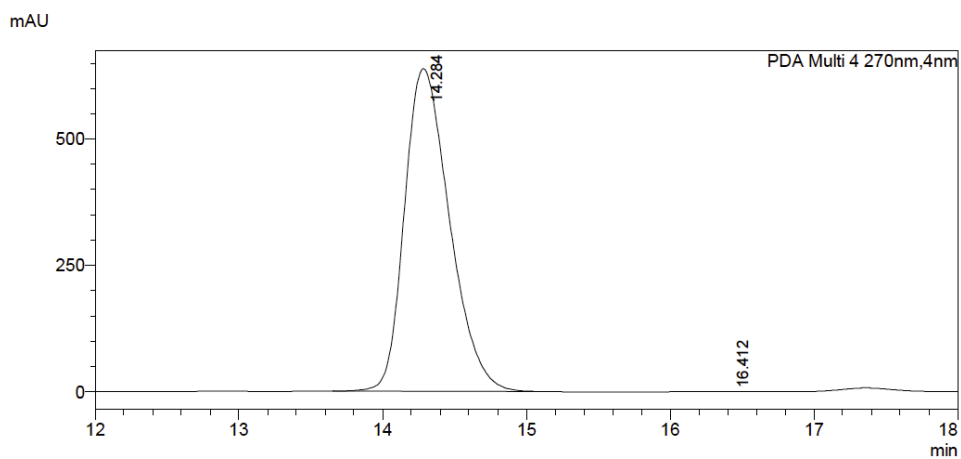




HPLC data for **21**: Chiralpak AD-H (90:10 hexane:IPA, flow rate 1.0 mLmin⁻¹, 270 nm, 30 °C) *t*_R (4*aS*,9*aR*): 14.3 min, *t*_R (4*aR*,9*aS*): 16.4 min, >99:1 er.

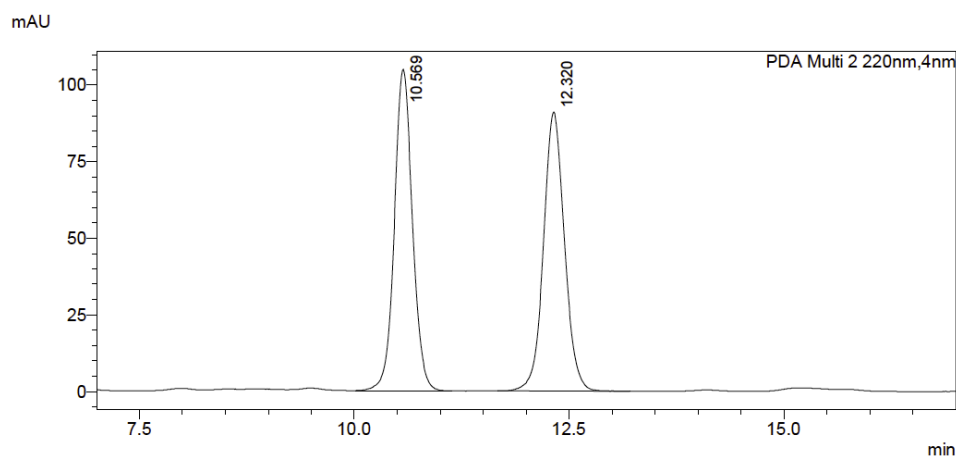
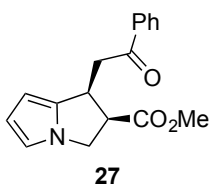


| PDA Ch4 270nm | | |
|---------------|-----------|---------|
| Peak# | Ret. Time | Area% |
| 1 | 14.315 | 49.947 |
| 2 | 15.739 | 50.053 |
| Total | | 100.000 |



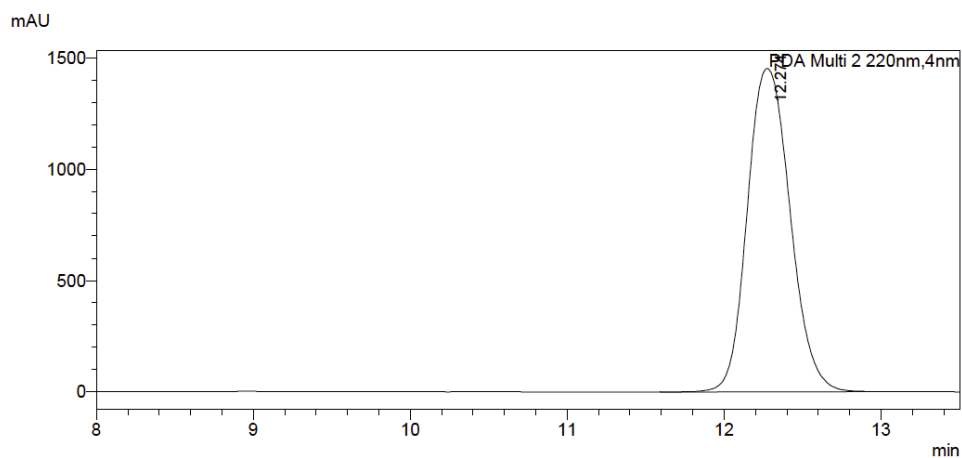
| PDA Ch4 270nm | | |
|---------------|-----------|---------|
| Peak# | Ret. Time | Area% |
| 1 | 14.284 | 99.941 |
| 2 | 16.412 | 0.059 |
| Total | | 100.000 |

HPLC data for **27**: Chiralpak AD-H (90:10 hexane:IPA, flow rate 1.0 mLmin⁻¹, 220 nm, 30 °C) t_R (1*S*,2*R*): 12.2 min, >99:1 er.



PDA Ch2 220nm

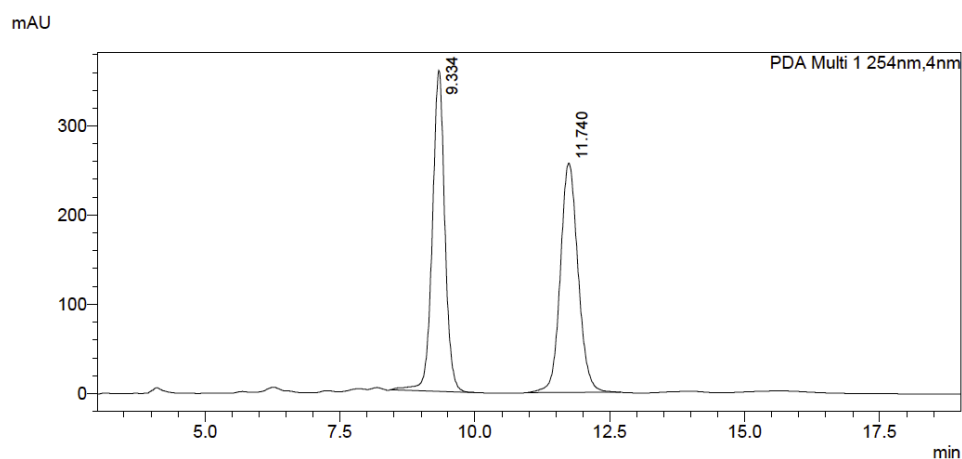
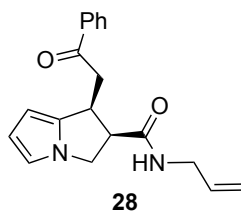
| Peak# | Ret. Time | Area% |
|-------|-----------|---------|
| 1 | 10.569 | 49.769 |
| 2 | 12.320 | 50.231 |
| Total | | 100.000 |



PDA Ch2 220nm

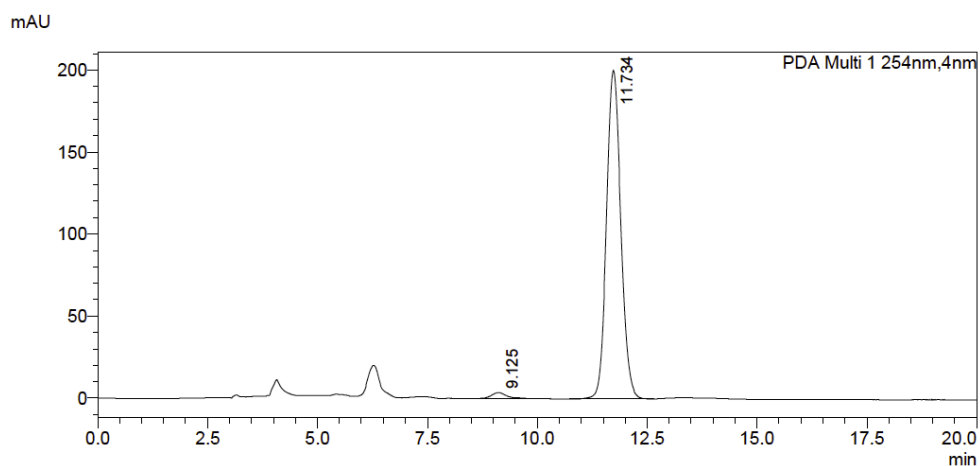
| Peak# | Ret. Time | Area% |
|-------|-----------|---------|
| 1 | 12.274 | 100.000 |
| Total | | 100.000 |

HPLC data for **28**: Chiralpak AD-H (80:20 hexane:IPA, flow rate 1.0 mLmin⁻¹, 254 nm, 30 °C) t_R (1*R*,2*S*): 9.1 min, t_R (1*S*,2*R*): 11.7 min, 98.5:1.5 er.



PDA Ch1 254nm

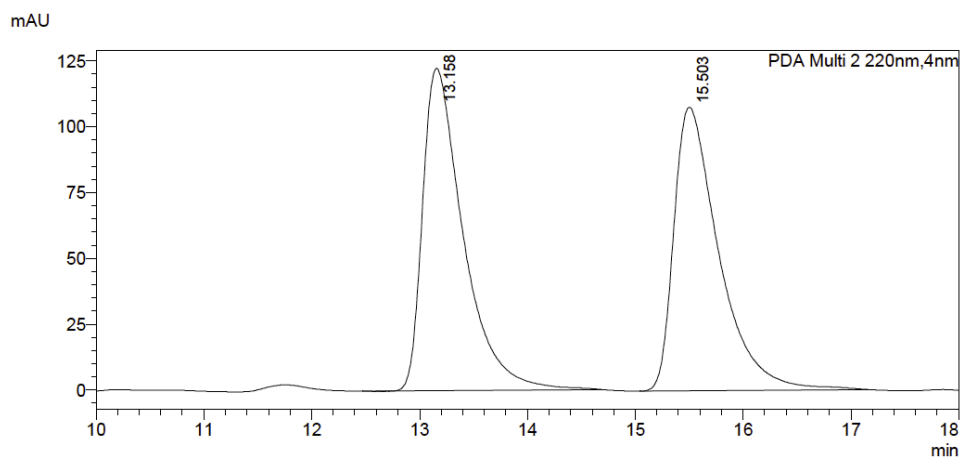
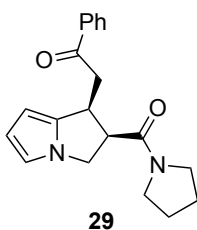
| Peak# | Ret. Time | Area% |
|-------|-----------|---------|
| 1 | 9.334 | 49.591 |
| 2 | 11.740 | 50.409 |
| Total | | 100.000 |



PDA Ch1 254nm

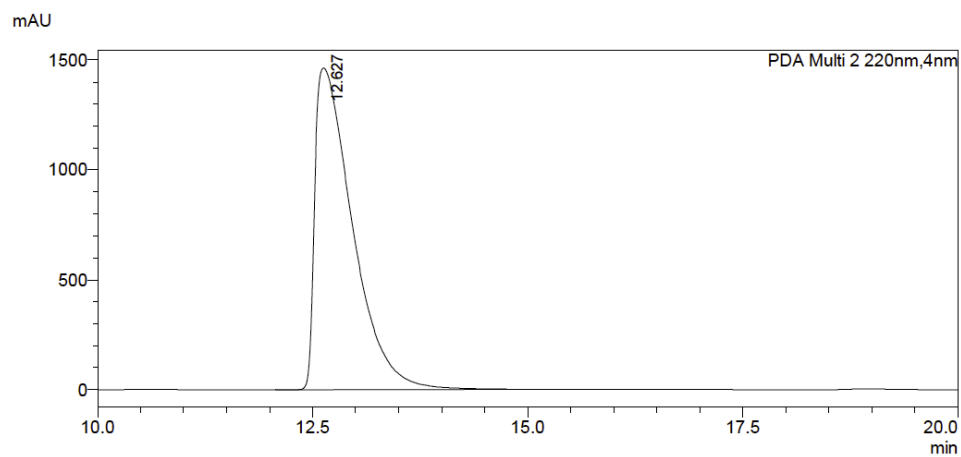
| Peak# | Ret. Time | Area% |
|-------|-----------|---------|
| 1 | 9.125 | 1.924 |
| 2 | 11.734 | 98.076 |
| Total | | 100.000 |

HPLC data for **29**: Chiralpak IB (90:10 hexane:IPA, flow rate 1.0 mLmin⁻¹, 220 nm, 30 °C) *t_R* (1*S*,2*R*): 12.6 min, >99:1 er.



PDA Ch2 220nm

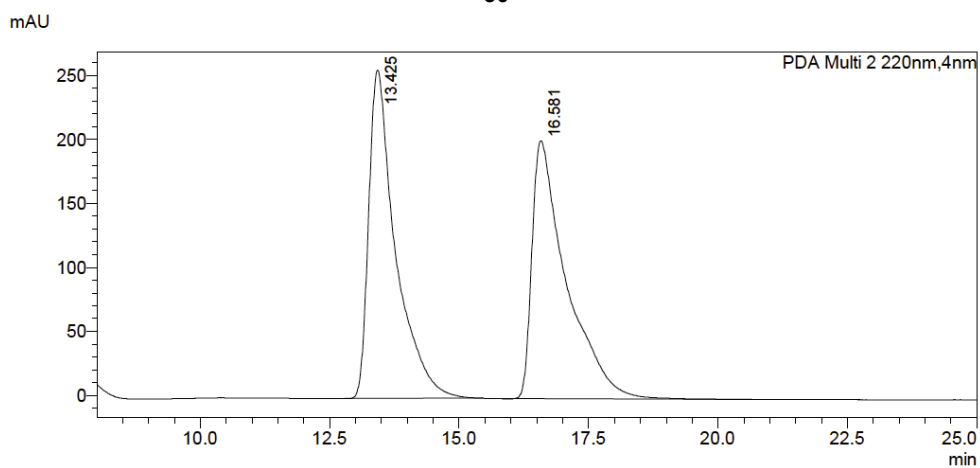
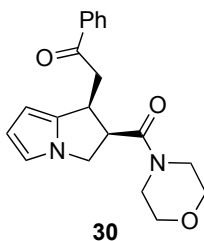
| Peak# | Ret. Time | Area% |
|-------|-----------|---------|
| 1 | 13.158 | 50.654 |
| 2 | 15.503 | 49.346 |
| Total | | 100.000 |



PDA Ch2 220nm

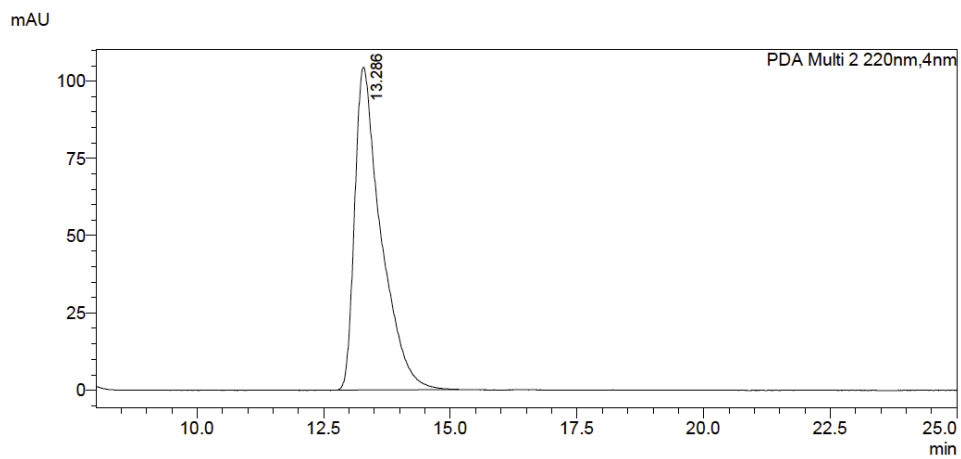
| Peak# | Ret. Time | Area% |
|-------|-----------|---------|
| 1 | 12.627 | 100.000 |
| Total | | 100.000 |

HPLC data for **30**: Chiralpak IA (80:20 hexane:IPA, flow rate 1.0 mLmin⁻¹, 220 nm, 30 °C) t_R (1*S*,2*R*): 13.3 min, >99:1 er.



PDA Ch2 220nm

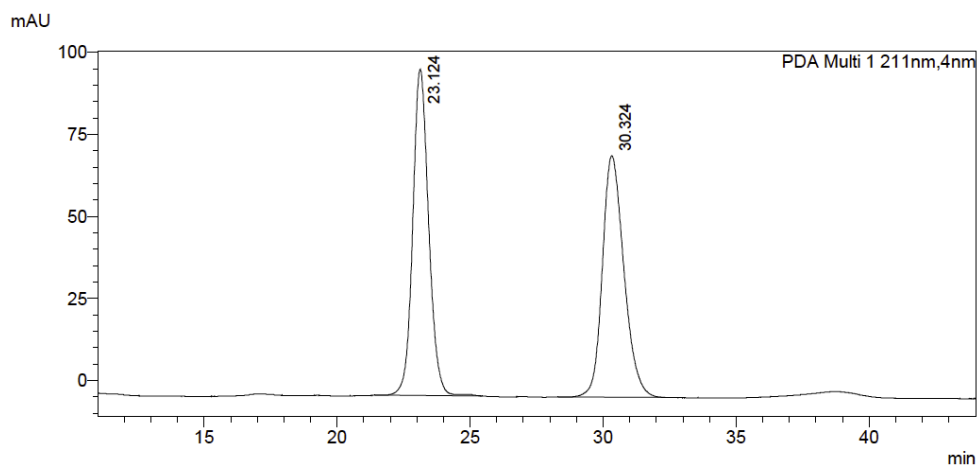
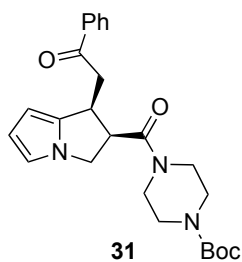
| Peak# | Ret. Time | Area% |
|-------|-----------|---------|
| 1 | 13.425 | 49.756 |
| 2 | 16.581 | 50.244 |
| Total | | 100.000 |



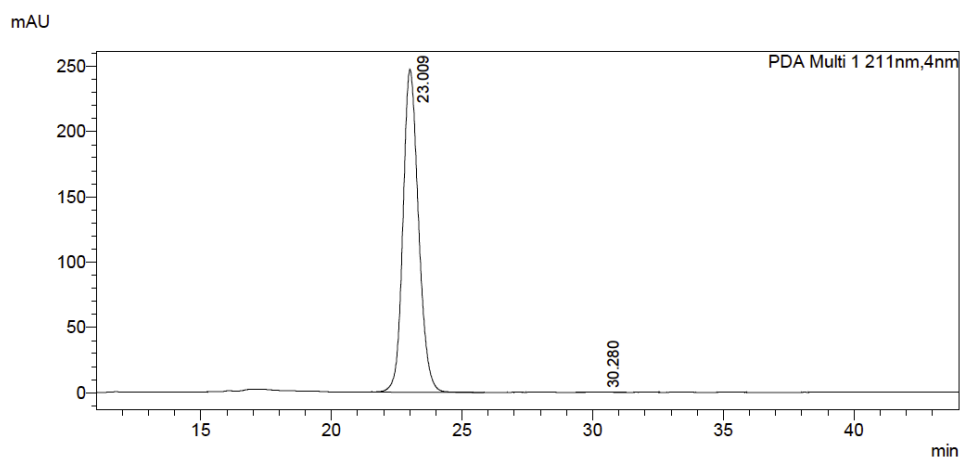
PDA Ch2 220nm

| Peak# | Ret. Time | Area% |
|-------|-----------|---------|
| 1 | 13.286 | 100.000 |
| Total | | 100.000 |

HPLC data for **31**: Chiralpak AD-H (90:10 hexane:IPA, flow rate 1.0 mLmin⁻¹, 211 nm, 30 °C) t_R (1*S*,2*R*): 23.0 min, t_R (1*R*,2*S*): 30.2 min, >99:1 er.

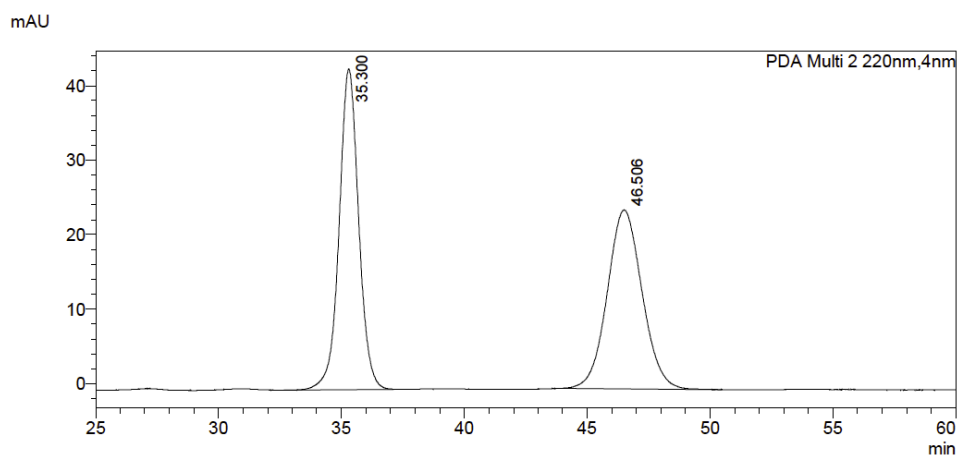
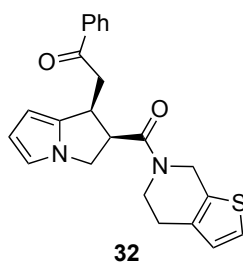


| PDA Ch1 211nm | | |
|---------------|-----------|---------|
| Peak# | Ret. Time | Area% |
| 1 | 23.124 | 49.912 |
| 2 | 30.324 | 50.088 |
| Total | | 100.000 |



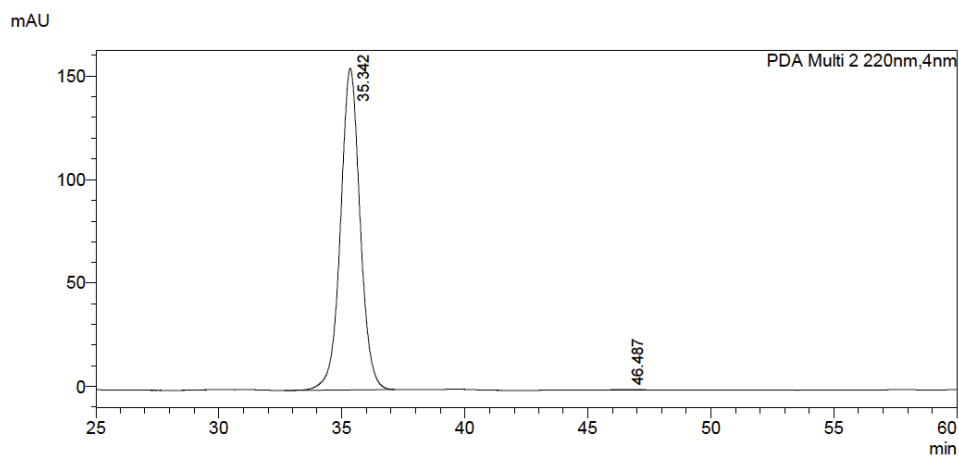
| PDA Ch1 211nm | | |
|---------------|-----------|---------|
| Peak# | Ret. Time | Area% |
| 1 | 23.009 | 99.905 |
| 2 | 30.280 | 0.095 |
| Total | | 100.000 |

HPLC data for **32**: Chiralpak AD-H (90:10 hexane:IPA, flow rate 1.0 mLmin⁻¹, 220 nm, 30 °C) t_R (1*S*,2*R*): 35.3 min, t_R (1*R*,2*S*): 46.5 min, >99:1 er.



PDA Ch2 220nm

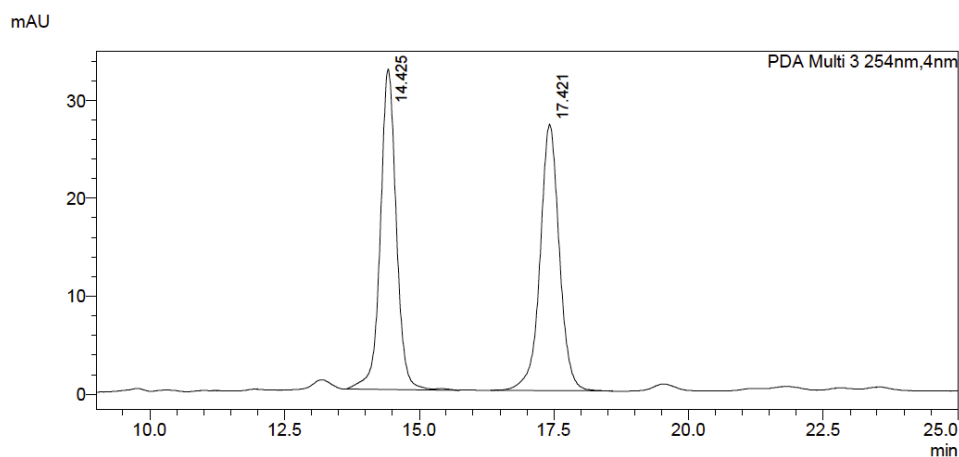
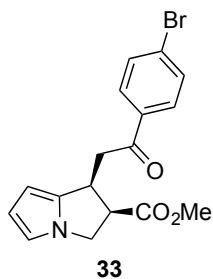
| Peak# | Ret. Time | Area% |
|-------|-----------|---------|
| 1 | 35.300 | 50.005 |
| 2 | 46.506 | 49.995 |
| Total | | 100.000 |



PDA Ch2 220nm

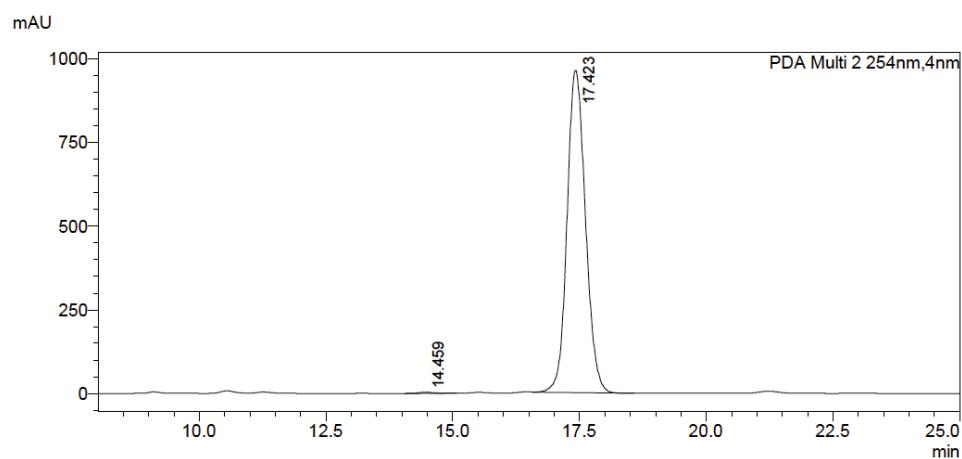
| Peak# | Ret. Time | Area% |
|-------|-----------|---------|
| 1 | 35.342 | 99.692 |
| 2 | 46.487 | 0.308 |
| Total | | 100.000 |

HPLC data for **33**: Chiralpak AD-H (90:10 hexane:IPA, flow rate 1.0 mLmin⁻¹, 254 nm, 30 °C) t_R (1*R*,2*S*): 14.5 min, t_R (1*S*,2*R*): 17.4 min, >99:1 er.



PDA Ch3 254nm

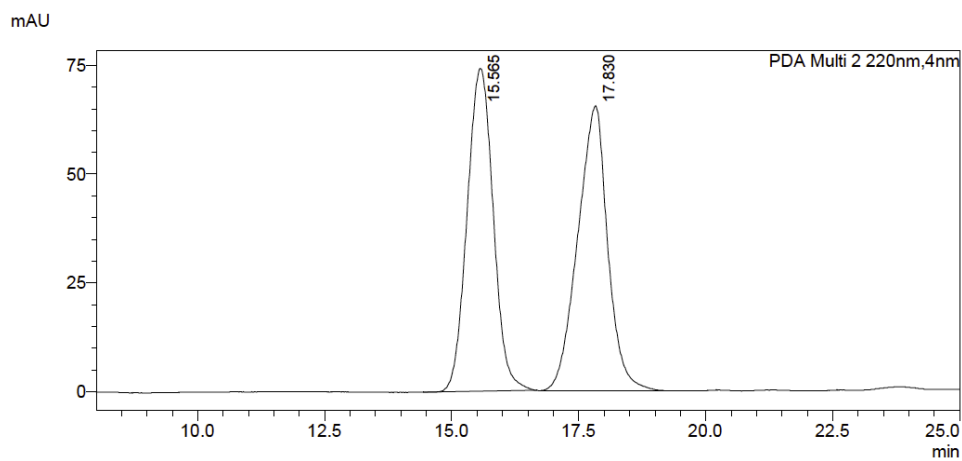
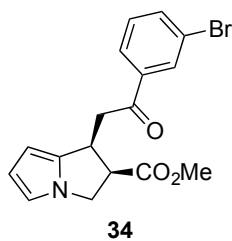
| Peak# | Ret. Time | Area% |
|-------|-----------|---------|
| 1 | 14.425 | 49.857 |
| 2 | 17.421 | 50.143 |
| Total | | 100.000 |



PDA Ch2 254nm

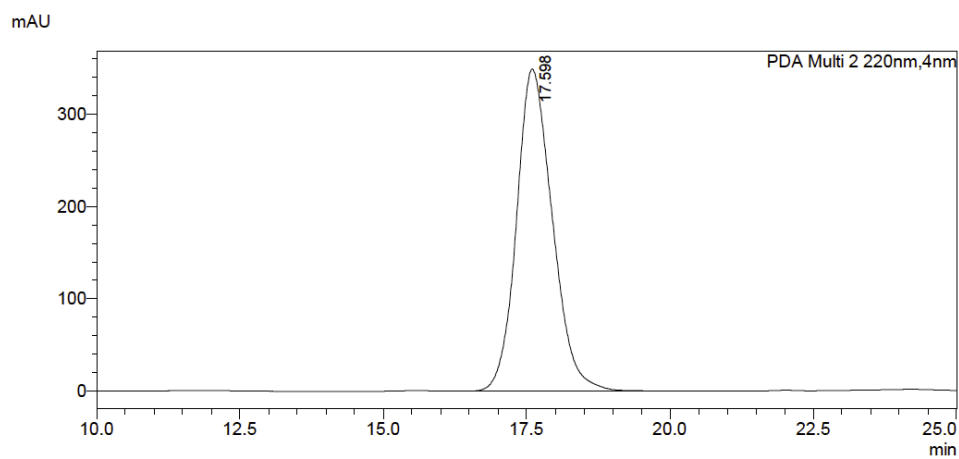
| Peak# | Ret. Time | Area% |
|-------|-----------|---------|
| 1 | 14.459 | 0.303 |
| 2 | 17.423 | 99.697 |
| Total | | 100.000 |

HPLC data for **34**: Chiralpak OD-H (90:10 hexane:IPA, flow rate 1.0 mLmin⁻¹, 220 nm, 30 °C) t_R (1*S*,2*R*): 17.6 min, >99:1 er.



PDA Ch2 220nm

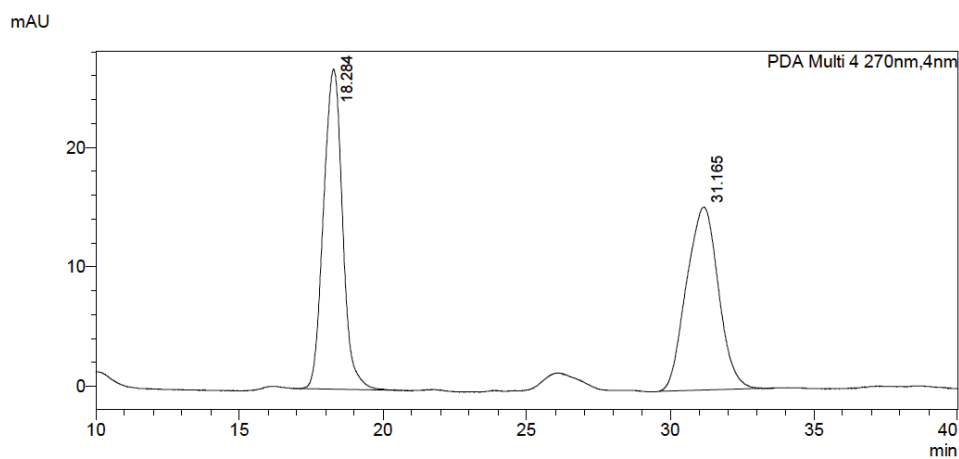
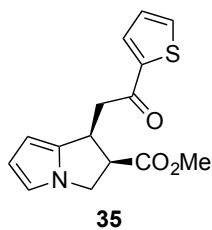
| Peak# | Ret. Time | Area% |
|-------|-----------|---------|
| 1 | 15.565 | 49.706 |
| 2 | 17.830 | 50.294 |
| Total | | 100.000 |



PDA Ch2 220nm

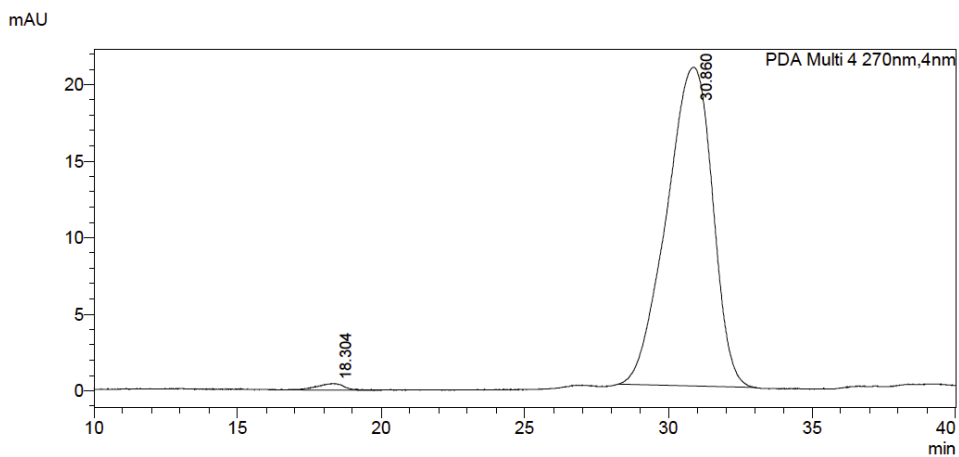
| Peak# | Ret. Time | Area% |
|-------|-----------|---------|
| 1 | 17.598 | 100.000 |
| Total | | 100.000 |

HPLC data for **35**: Chiralpak OD-H (90:10 hexane:IPA, flow rate 1.0 mLmin⁻¹, 270 nm, 30 °C) t_R (1*R*,2*S*): 18.3 min, t_R (1*S*,2*R*): 30.9 min, 99:1 er.



PDA Ch4 270nm

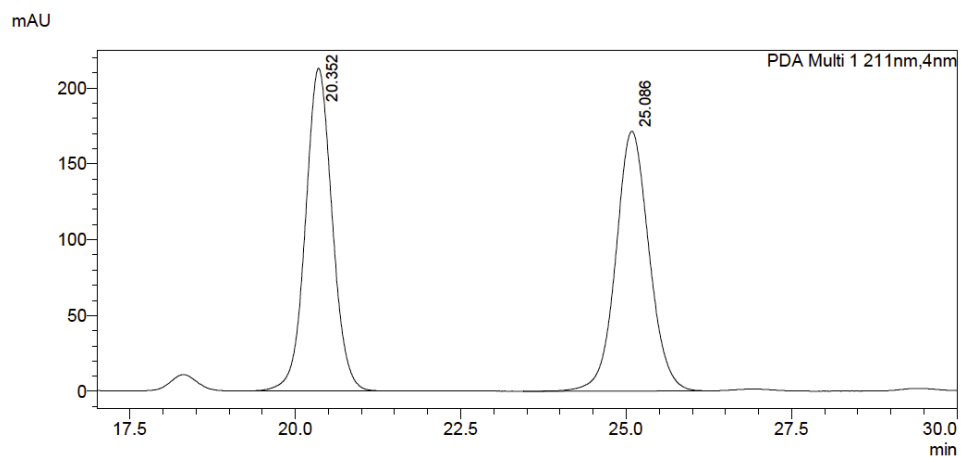
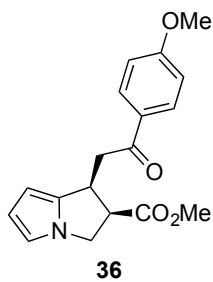
| Peak# | Ret. Time | Area% |
|-------|-----------|---------|
| 1 | 18.284 | 50.922 |
| 2 | 31.165 | 49.078 |
| Total | | 100.000 |



PDA Ch4 270nm

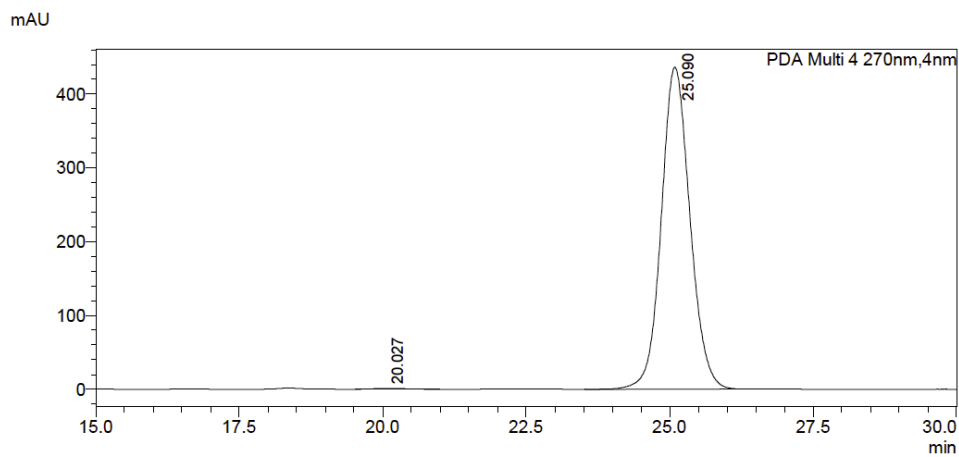
| Peak# | Ret. Time | Area% |
|-------|-----------|---------|
| 1 | 18.304 | 1.150 |
| 2 | 30.860 | 98.850 |
| Total | | 100.000 |

HPLC data for **36**: Chiralpak AD-H (90:10 hexane:IPA, flow rate 1.0 mLmin⁻¹, 270 nm, 30 °C) t_R (1*R*,2*S*): 20.0 min, t_R (1*S*,2*R*): 25.1 min, >99:1 er.



PDA Ch1 211nm

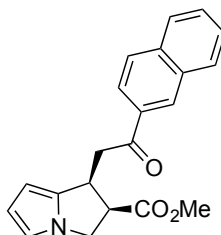
| Peak# | Ret. Time | Area% |
|-------|-----------|---------|
| 1 | 20.352 | 50.000 |
| 2 | 25.086 | 50.000 |
| Total | | 100.000 |



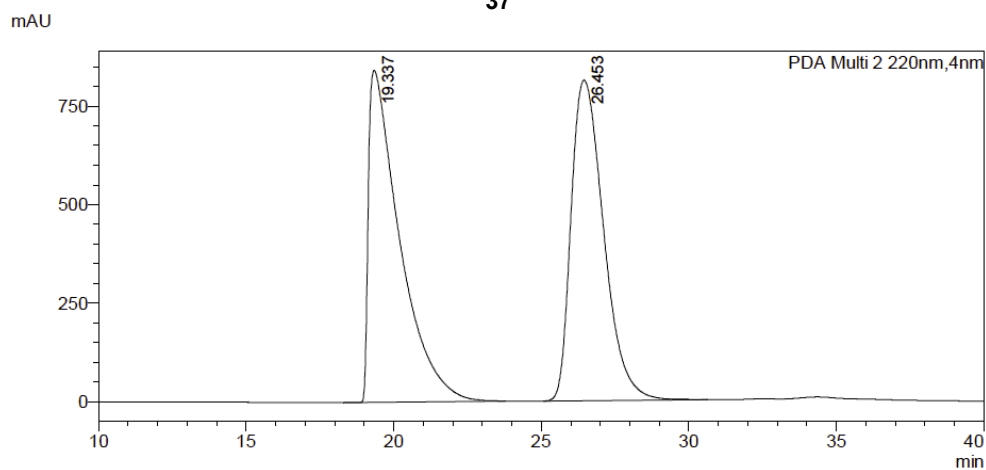
PDA Ch4 270nm

| Peak# | Ret. Time | Area% |
|-------|-----------|---------|
| 1 | 20.027 | 0.285 |
| 2 | 25.090 | 99.715 |
| Total | | 100.000 |

HPLC data for **37**: Chiralpak OD-H (90:10 hexane:IPA, flow rate 1.0 mLmin⁻¹, 220 nm, 30 °C) t_R (1*R*,2*S*): 20.9 min, t_R (1*S*,2*R*): 27.0 min, >99:1 er.

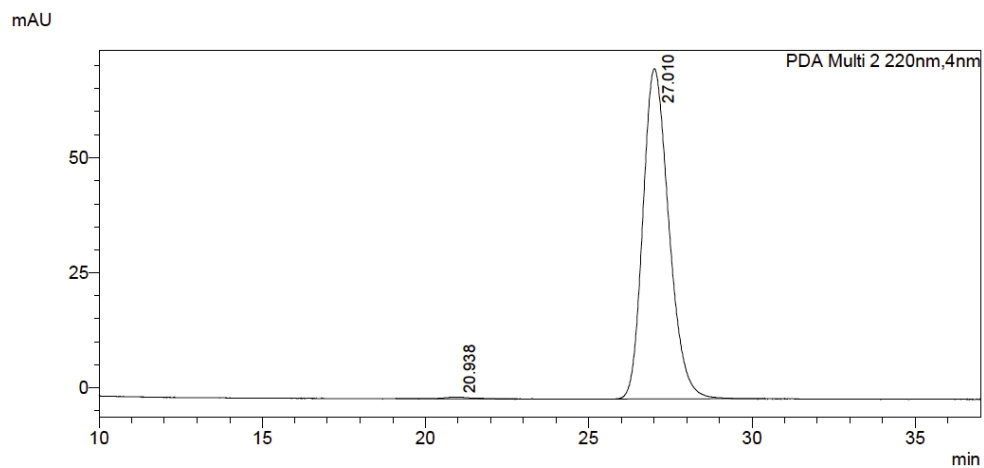


37



PDA Ch2 220nm

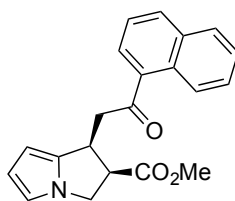
| Peak# | Ret. Time | Area% |
|-------|-----------|---------|
| 1 | 19.337 | 49.762 |
| 2 | 26.453 | 50.238 |
| Total | | 100.000 |



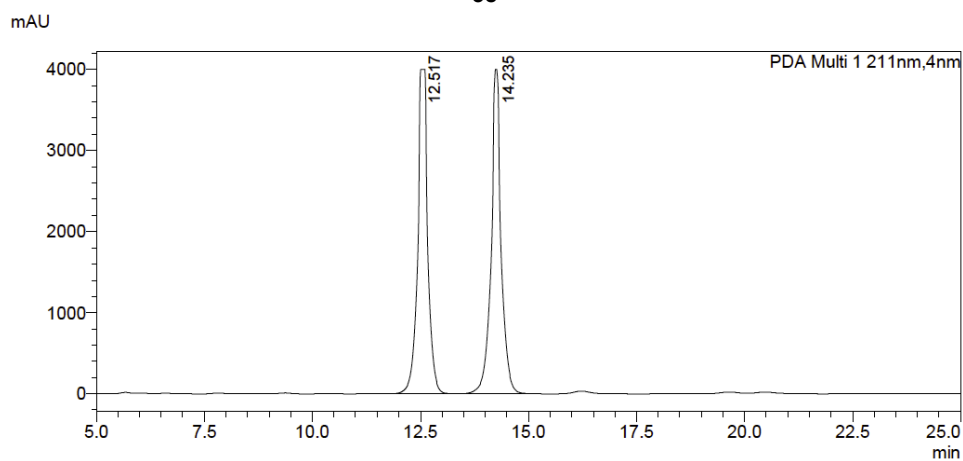
PDA Ch2 220nm

| Peak# | Ret. Time | Area% |
|-------|-----------|---------|
| 1 | 20.938 | 0.600 |
| 2 | 27.010 | 99.400 |
| Total | | 100.000 |

HPLC data for **38**: Chiralpak AD-H (90:10 hexane:IPA, flow rate 1.0 mLmin⁻¹, 211 nm, 30 °C) *t_R* (1*R*,2*S*): 12.5 min, *t_R* (1*S*,2*R*): 14.2 min, >99:1 er.

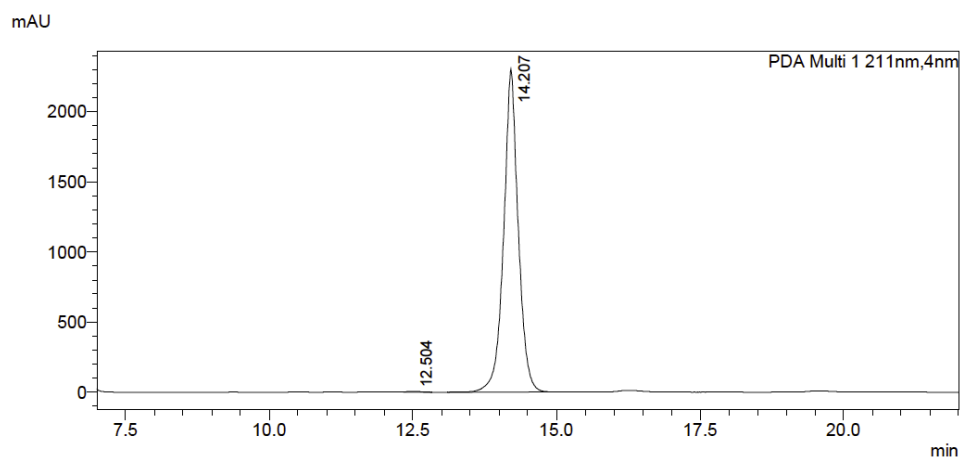


38



PDA Ch1 211nm

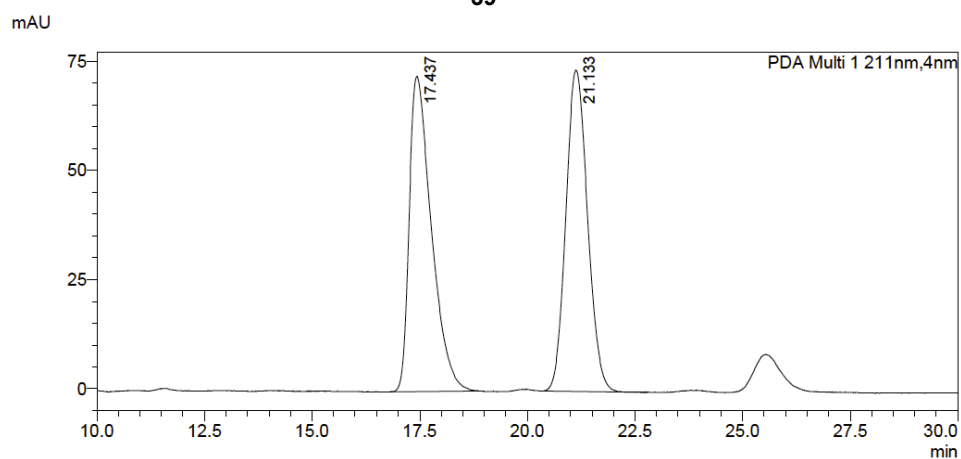
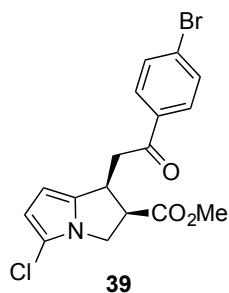
| Peak# | Ret. Time | Area% |
|-------|-----------|---------|
| 1 | 12.517 | 50.402 |
| 2 | 14.235 | 49.598 |
| Total | | 100.000 |



PDA Ch1 211nm

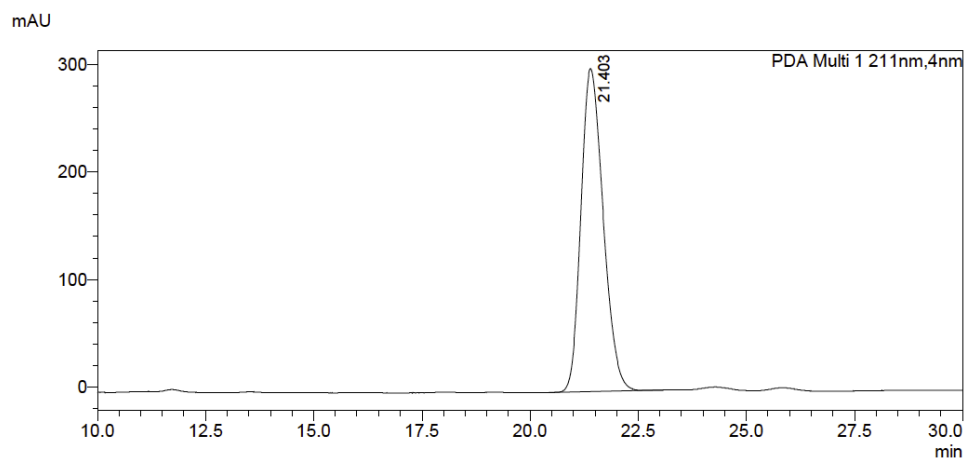
| Peak# | Ret. Time | Area% |
|-------|-----------|---------|
| 1 | 12.504 | 0.241 |
| 2 | 14.207 | 99.759 |
| Total | | 100.000 |

HPLC data for **39**: Chiralpak OD-H (90:10 hexane:IPA, flow rate 1.0 mLmin⁻¹, 211 nm, 30 °C) t_R (1*S*,2*R*): 21.4 min, >99:1 er.



PDA Ch1 211nm

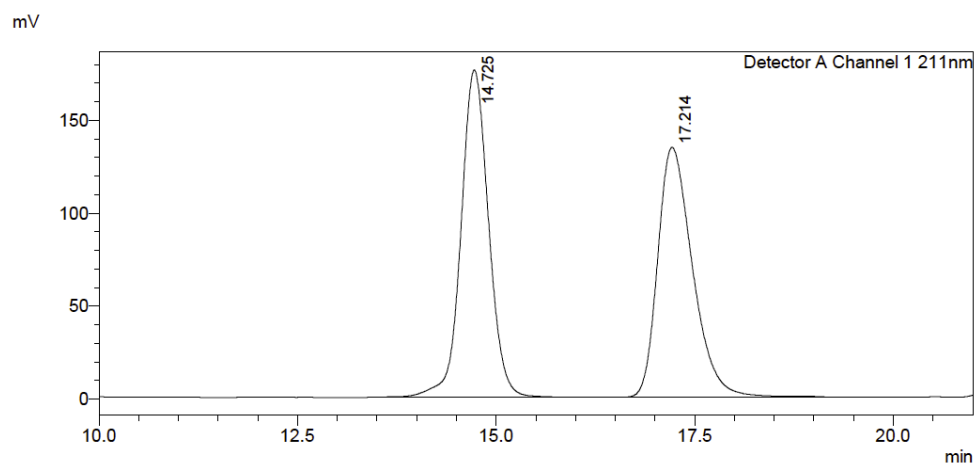
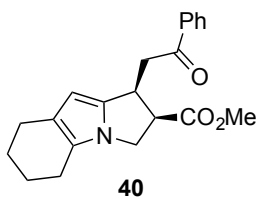
| Peak# | Ret. Time | Area% |
|-------|-----------|---------|
| 1 | 17.437 | 50.073 |
| 2 | 21.133 | 49.927 |
| Total | | 100.000 |



PDA Ch1 211nm

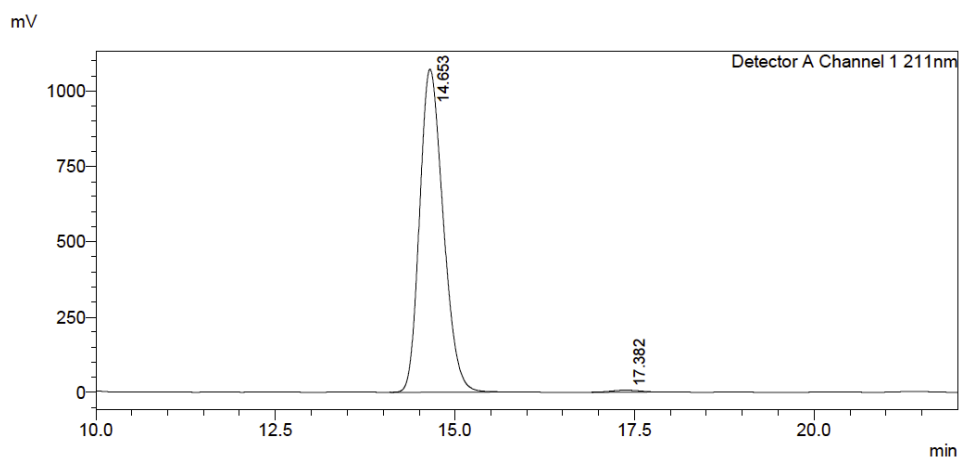
| Peak# | Ret. Time | Area% |
|-------|-----------|---------|
| 1 | 21.403 | 100.000 |
| Total | | 100.000 |

HPLC data for **40**: Chiralpak IC (90:10 hexane:IPA, flow rate 1.0 mLmin⁻¹, 211 nm, 30 °C) *t_R* (1*S*,2*R*): 14.7 min, *t_R* (1*R*,2*S*): 17.4 min, >99:1 er.



Detector A Channel 1 211nm

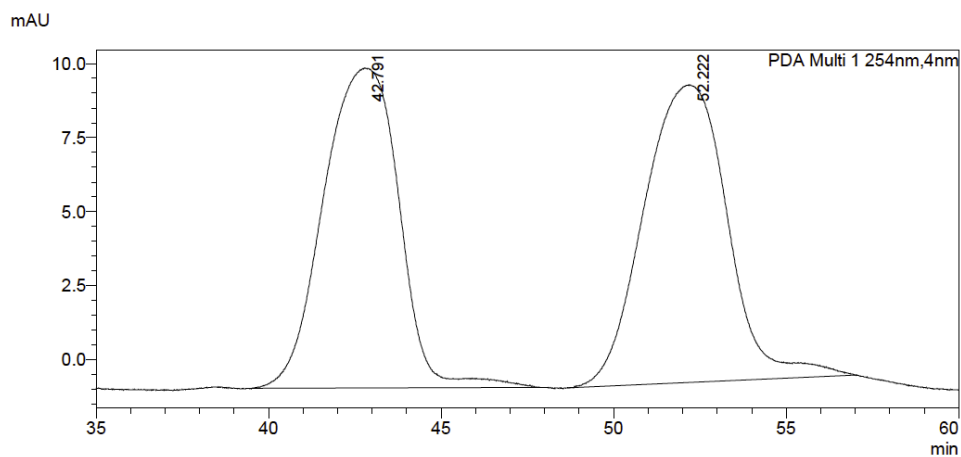
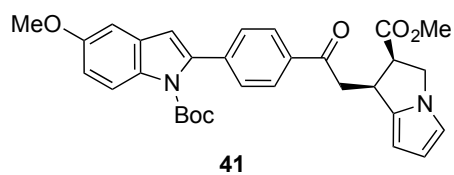
| Peak# | Ret. Time | Area% |
|-------|-----------|---------|
| 1 | 14.725 | 50.880 |
| 2 | 17.214 | 49.120 |
| Total | | 100.000 |



Detector A Channel 1 211nm

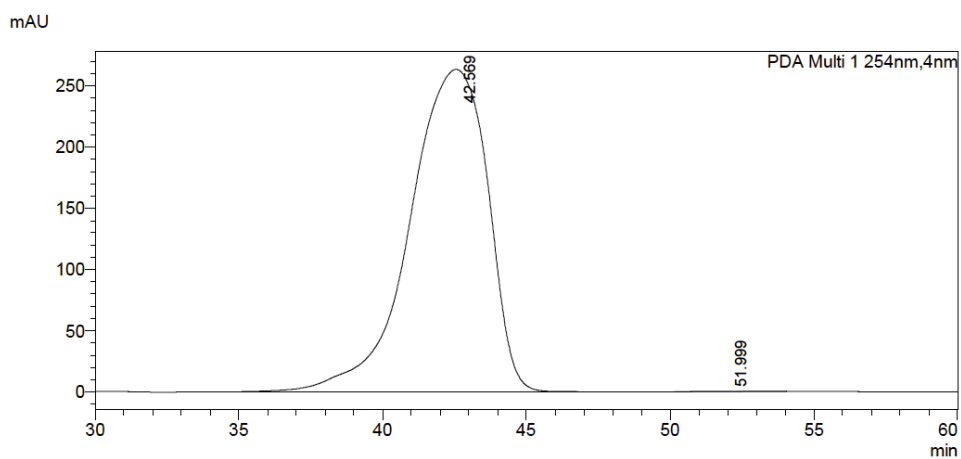
| Peak# | Ret. Time | Area% |
|-------|-----------|---------|
| 1 | 14.653 | 99.210 |
| 2 | 17.382 | 0.790 |
| Total | | 100.000 |

HPLC data for **41**: Chiralpak AD-H (90:10 hexane:IPA, flow rate 1.0 mLmin⁻¹, 254 nm, 30 °C) t_R (1*S*,2*R*): 42.6 min, t_R (1*R*,2*S*): 52.0 min, >99:1 er.



PDA Ch1 254nm

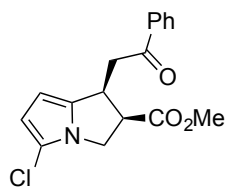
| Peak# | Ret. Time | Area% |
|-------|-----------|---------|
| 1 | 42.791 | 49.259 |
| 2 | 52.222 | 50.741 |
| Total | | 100.000 |



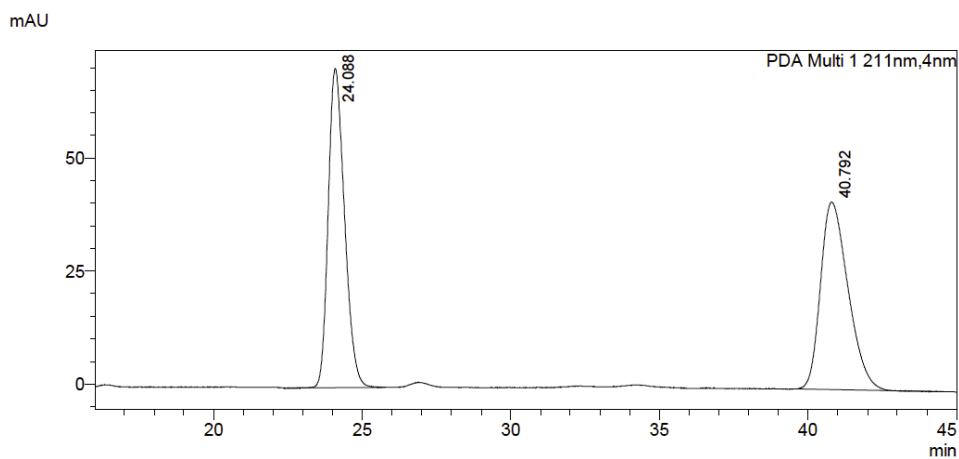
PDA Ch1 254nm

| Peak# | Ret. Time | Area% |
|-------|-----------|---------|
| 1 | 42.569 | 99.938 |
| 2 | 51.999 | 0.062 |
| Total | | 100.000 |

HPLC data for **42**: Chiralpak OD-H (90:10 hexane:IPA, flow rate 1.0 mLmin⁻¹, 211 nm, 30 °C) t_R (1*R*,2*S*): 24.2 min, t_R (1*S*,2*R*): 39.7 min, >99:1 er.

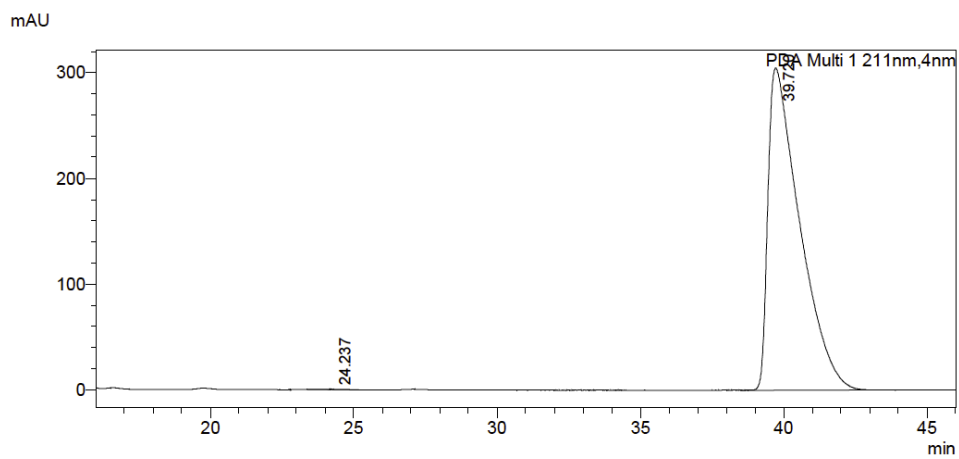


42



PDA Ch1 211nm

| Peak# | Ret. Time | Area% |
|-------|-----------|---------|
| 1 | 24.088 | 50.063 |
| 2 | 40.792 | 49.937 |
| Total | | 100.000 |



PDA Ch1 211nm

| Peak# | Ret. Time | Area% |
|-------|-----------|---------|
| 1 | 24.237 | 0.078 |
| 2 | 39.720 | 99.922 |
| Total | | 100.000 |